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Minimising potentially inappropriate polypharmacy in community living older people:

A multi-phase, mixed methods study to develop and pilot a general practitioner-led deprescribing intervention in primary care

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Abstract

Background

Polypharmacy-related harm affects many older Australians. Clinician supervised withdrawal or dose reduction of potentially inappropriate medicines (PIMs), defined as deprescribing, aims to reduce this harm. General practitioners (GPs), with the support of consultant pharmacists (CPs), are well positioned to initiate deprescribing in community living older people with potentially inappropriate polypharmacy. Effecting prescribing change is difficult however, and there is little research into GP-led deprescribing interventions in this patient group which evaluates clinicians' barriers and enablers to change.

Research aims

To: 1) investigate factors which shape prescribers' behaviour towards continuing or discontinuing PIMs in adults; 2) explore the views of GPs and CPs about potentially inappropriate polypharmacy and the reasoning they apply to deprescribing in community living older people; and 3) investigate the feasibility, effectiveness and safety of a GP-led deprescribing intervention involving such people in primary care.

Methodology

A sequential, exploratory mixed methods design with three phases which aligned to three research aims was used. Phase One involved a systematic review and thematic synthesis of studies exploring prescribers' perceived barriers and enablers to minimising chronically-prescribed PIMs in adults.

Phase Two, a qualitative investigation, comprised seven focus group discussions involving 32 GPs and 15 CPs recruited from within metropolitan Southeast Queensland using a mix of convenience and snowball sampling. Data were analysed thematically using the Framework method.

Phase One and Two findings informed the design of the multifaceted GP-led deprescribing intervention piloted in Phase Three. A pragmatic, controlled pre-post mixed methods design was used to evaluate intervention feasibility, effectiveness and safety. Convenience sampling was used to recruit five general practices and 22 clinicians. Seventy-eight intervention and 67 usual care patients were consecutively sampled. Quantitative and

qualitative data were collected at both clinician and patient levels. The primary outcome was the mean difference in the number of regular medications deprescribed (i.e. ceased or dose-reduced) per patient over the 18-week study period. Secondary outcomes comprised intervention impact on patients' medication regimens, self-reported health status, attitudes towards medicines and deprescribing, and GP/patient reports of actual or suspected adverse outcomes or experiences. Qualitative data from semi-structured interviews were used to help explain quantitative results and the intervention's feasibility, acceptability and sustainability.

Results

The systematic review addressing the first research aim of exploring prescribers' perceived barriers and enablers to minimising PIMs comprised studies mostly exploring primary care physicians' perspectives on managing older, community living adults. Four major themes emerged: problem awareness; perceived value of ceasing versus continuing PIMs; self-efficacy regarding clinicians' ability to alter prescribing; and feasibility of altering prescribing in routine care environments given external constraints.

Two major themes were derived in response to the second thesis aim regarding GPs' and CPs' views and reasoning about potentially inappropriate polypharmacy: 1) *Working through uncertainty* encapsulated the immense complexity clinicians face when assessing an older person with potentially inappropriate polypharmacy, such that weighing harm against benefit in absolute terms at the level of the individual was perceived as unfeasible. However, strategies and circumstances were identified that could mitigate this uncertainty; 2) *Perceived risk as a frame of reference* referred to the dichotomised view that deprescribing was a risk to be avoided or risk to be reconciled, with tipping points in risk perception identified which might trigger action towards deprescribing.

The exploratory pilot study addressed the third aim of investigating the feasibility, effectiveness and safety of the multifaceted intervention in community living older people in primary care. The mean difference between intervention and usual care groups in the number of regular medications deprescribed per patient was -0.55, 95%CI -0.897 to -0.212, p = 0.002. The respective proportions of patients having at least one medication deprescribed were 52.6% versus 28.4%, p = 0.005, such that intervention patients were 2.3 times more likely to have at least one regular medication deprescribed (incidence rate ratio

[IRR] 2.3; 95% CI 1.297-3.964, p = 0.004). The intervention was not associated with any reported harm or deterioration in health-related quality of life which may have resulted from injudicious attempts at deprescribing appropriate medication. A subset of intervention patients reported greater certainty in the necessity and appropriateness of their medications at study completion. Qualitative data showed the majority of GPs and patients derived satisfaction from the process of medication review and consultation during dedicated deprescribing appointment/s, irrespective of whether the outcome of successful medication withdrawal was achieved. Whilst seen as feasible in the short-term, GPs gave mixed responses regarding the sustainability of the intervention in routine care.

Conclusions and recommendations

This multi-phase, mixed methods study demonstrated immense diversity in clinicians' perceived barriers and enablers to deprescribing in community living older people. The multifaceted intervention addressing local barriers was feasible and safe in the short-term and conferred a clinically modest deprescribing effect. Further research into the long-term effectiveness and safety of deprescribing interventions targeting community living older people at high-risk of medication misadventure is warranted.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, financial support and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my higher degree by research candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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Publications during candidature

Peer-reviewed papers

1. Anderson K, Foster M, Freeman C, Luetsch K, Scott I. Negotiating “Unmeasurable Harm and Benefit”. Qual Health Res. 2017:1049732316687732.
2. Anderson K, Foster MM, Freeman CR, Scott IA. A multifaceted intervention to reduce inappropriate polypharmacy in primary care: research co-creation opportunities in a pilot study. Med J Aust. 2016;204(7 Suppl): S41-4.
3. Anderson K, Freeman C, Rowett D, Burrows J, Scott I, Rigby D. Polypharmacy, deprescribing and shared decision-making in primary care: the role of the accredited pharmacist. J Pharm Pract Res. 2015;45(4):446-9.
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7. Scott IA, Anderson K, Freeman CR, Stowasser DA. First do no harm: a real need to deprescribe in older patients. Med J Aust. 2014;201(7):390-2.

Conference abstracts

1. Anderson K, Freeman CR, Foster MM, Scott IA. GP-led deprescribing in older people with polypharmacy in primary care. Oral presentation at the 2017 Primary Health Care Research Conference, Brisbane, Australia.
2. Anderson K, Freeman CR, Foster MM, Scott IA. Optimising medicines through deprescribing in primary care in Australia. Oral presentation at the 2016 Royal College of Surgeons Ireland General Practice Divisional Summer Series, Dublin, Ireland.

3. Anderson K, Foster MM, Freeman CR, Luetsch K, Scott IA. Why we fail to act – Perspectives of general practitioners and consultant pharmacists on deprescribing in primary care. Oral presentation at the 2016 Preventing Overdiagnosis Conference, Barcelona, Spain.
4. Anderson K, Foster MM, Freeman CR, Luetsch K, Scott IA. Negotiating unmeasurable harm and benefit – Clinicians' perspectives on deprescribing in the primary care setting. Oral presentation at the 2016 3rd Australian Deprescribing Network Forum, Melbourne, Australia.
5. Anderson K, Foster MM, Freeman CR, Luetsch K, Scott IA. Negotiating 'unmeasurable harms and benefits' - General practitioners' and consultant pharmacists' barriers and enablers to deprescribing in primary care. Poster presentation at the 2016 National Medicines Symposium (NMS), Canberra, Australia.
6. Anderson K, Foster MM, Freeman CR, Luetsch K, Scott IA. GPs' & pharmacists' barriers and enablers to deprescribing in older people in primary care. Oral presentation at the 2016 3rd International Primary Health Care Reform Conference, Brisbane, Australia.
7. Anderson K, Freeman CR, Stowasser D, Scott IA. Prescribers' barriers and enablers to deprescribing. Oral presentation at the 2015 SHPA Medicines Management Conference - Deprescribing COSP, Melbourne, Australia.
8. Anderson K, Freeman CR, Stowasser D, Scott IA. Optimising medicines through deprescribing in primary care. Oral presentation at the 2015 Australian Deprescribing Network Forum and National Stakeholders Meeting, Sydney, Australia.
9. Anderson K, Freeman C, Stowasser D, Scott I. To prescribe or deprescribe potentially inappropriate medication/s in adults? A systematic review of prescribers' perspectives. Poster presentation at the 2014 Primary Health Care Research Conference, Canberra, Australia.
10. Anderson K, Stowasser D, Freeman CR, Scott IA. To prescribe or deprescribe potentially inappropriate medication/s in adults? A qualitative systematic review of

prescribers' perspectives. Oral presentation at the 2014 National Medicines Symposium, Brisbane, Australia.

11. Anderson K, Stowasser D, Freeman CR, Scott IA. To prescribe or deprescribe potentially inappropriate medication/s in adults? Interim results of a qualitative systematic review of prescribers' perspectives. Oral presentation at the 2014 Australian Deprescribing Network Forum, Brisbane, Australia.

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Contributor	Statement of contribution
Anderson, K (Candidate)	Search & question refinement (80%) Data analysis & theme development (90%) Preparation of first manuscript (100%)
Stowasser, D (Associate supervisor)	Search & question refinement (5%) Data analysis & theme development (10%) Manuscript revisions (10%)
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Anderson, K (Candidate)	Data collection (80%) Data analysis & theme development (85%) Preparation of first manuscript (100%)
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Scott, I (Principal supervisor)	Theme refinement (30%) Manuscript revisions (30%)

Contributions by others to the thesis

The PhD candidate was primarily responsible for: refining the conceptual development and design of the three-phased mixed methods study; gaining ethical approval; participant recruitment; data collection; data analysis; interpretation and synthesis of research findings; and thesis preparation.

The Principal Supervisor, A/Prof Ian Scott, as one of the Chief Investigators of the National Health and Medical Research Council Centre of Research Excellence (CRE): Quality & Safety in Integrated Primary-Secondary Care, first conceptualised the three-phased mixed methods project on deprescribing. Both A/Prof Ian Scott and Professor Michele Foster were influential in securing grant funding for the CRE which supported this research.

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To the best of my knowledge and belief, no person who has offered contributions consistent with the above has been excluded as an author. Persons who have contributed to the work but not at the level which constitutes authorship have been acknowledged in text as appropriate.

Statement of parts of the thesis submitted to qualify for the award of another degree

None.

Research Involving Human or Animal Subjects

The following ethics approvals were obtained from the University of Queensland Institutional Human Research Ethics Unit for this research:

- 'An Exploration of GPs' and Accredited Pharmacists' Views of Deprescribing in Community-Based Older People with Polypharmacy' - Approval Number 2014001296;
- 'Optimising Medicines Through Deprescribing in Community-Based, Older People with Polypharmacy – an Exploratory Mixed-Methods Study' – Approval Number 2015000044;
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Copies of the ethics approval letters are included in Appendix 1.

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Polypharmacy, deprescribing, primary care, older people.

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Fields of Research (FoR) Classification

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FoR code: 1117, Public Health and Health Services, 50%

Table of Contents

List of Figures

List of Tables

List of abbreviations used in the thesis

ADEs	Adverse Drug Events
AOR	Adjusted Odds Ratio
CMR	Comprehensive Medication Review
CI	Confidence Interval
CPs	Consultant Pharmacists
CRE	Centre of Research Excellence
ED	Emergency Department
GPs	General Practitioners
HMR	Home Medicines Review
HRQoL	Health-Related Quality of Life
IQR	Interquartile Range
IRR	Incidence Rate Ratio
IT	Information Technology
MAI	Medication Appropriateness Index
MD	Mean Difference
MRC	Medical Research Council
NH	Nursing Home
OECD	Organisation for Economic Cooperation and Development
OR	Odds Ratio
PBS	Pharmaceutical Benefits Scheme
PIMs	Potentially Inappropriate Medicines/Medications
PIP	Potentially Inappropriate Prescribing
PRN	Pro re nata (referring to intermittent or ‘as required’ medications)
QH	Queensland Health

QUM	Quality Use of Medicines
RACF	Residential Aged Care Facilities
RACGP	Royal Australian College of General Practitioners
RCT	Randomised Controlled Trial
SD	Standard Deviation
SEQ	South East Queensland
START	Screening Tool to Alert doctors to Right (i.e. appropriate, indicated) Treatments
STOPP	Screening Tool of Older People's potentially inappropriate Prescriptions

Chapter 1 Introduction

There is an urgent and growing need to minimise iatrogenic harm from potentially inappropriate polypharmacy in ageing populations with multimorbidity. The single biggest risk factor for taking one or more potentially inappropriate medicines (PIMs) is the number of medicines prescribed. (1, 2) 'Deprescribing' has been proposed as way to minimise potentially inappropriate polypharmacy. It is defined as the proactive, systematic process of identifying and discontinuing medicines where the actual or potential harms of medicines outweigh the benefits, after giving consideration to an individual patient's care goals, physical and mental function, life expectancy, values, and preferences. (3) Although deprescribing is a relatively new term in the medical lexicon, appropriate cessation or reduction of medication is a long accepted component of competent prescribing. (4, 5)

General practitioners (GPs) play a central role in the coordination and delivery of healthcare to the Australian community. (6) They have a critical role in the management of patients with multimorbidity and associated polypharmacy and attendant risks, all of which increase with age. (7) Deprescribing is a challenging and complex intervention however, complicated by many factors at the patient, provider and health system levels. (8, 9) This study focussed on a GP-led intervention to minimise potentially inappropriate polypharmacy in community living older people in primary care. Specifically, the aim was to develop and pilot a multifaceted GP-led intervention to minimise potentially inappropriate polypharmacy in this patient group, addressing GP and consultant pharmacist (CP) barriers and enablers to deprescribing in routine care.

1.1 Rationale for this study

Like other OECD countries, Australia's population is ageing. Between 2014 and 2064, the proportion of older people (those aged 65 years or more) is projected to increase from 15% to 23% of Australia's population and the number of very old people (aged 85 years or more) is projected to increase from 1.9% to 5%. (10, 11) The overwhelming majority of older individuals, including the very old, reside in private dwellings in the community, not in residential aged care. (12) This is likely to continue, given the policy setting over the past decade in Australia, to increasingly support older people 'ageing in place' (i.e. residing in their own homes, rather than transitioning to care) which is in line with individual preferences and is more economically sustainable. (13)

Older people are more likely to have multiple chronic conditions and take multiple concurrent medicines. (14) According to recent Australian general practice data, 57% of people aged 65 years and older had three or more chronic conditions (defined as multimorbidity) and almost 10% had seven or more chronic conditions. (15) One in two older Australians report taking five or more prescription, over-the-counter and/or complementary medicines daily, with 20% taking more than ten. (16, 17) Despite representing 13% of the population, people 65 years and over contributed to more than half of all PBS expenditure between 2006 and 2011, and half of this expenditure was related to people 75 years and older. (18)

Safe and effective prescribing in older people is particularly challenging. A range of pharmacokinetic and pharmacodynamic changes increase exposure to adverse medication effects and diminish the predictability of response to therapy. (19) This is compounded by inadequate research and knowledge of geriatric therapeutics and toxicology, due to the under-representation/exclusion of older people from most clinical trials. (20, 21)

The appropriate prescription and use of medicines can extend the duration and improve the quality of life in older people. The use of PIMs however, the probability of which increases with the number of concomitant medications prescribed, is associated with significant harm including adverse drug events (ADEs), hospital presentations, poorer health related quality of life and functioning, geriatric syndromes (e.g., delirium, falls, or frailty) and even death. (22-26). It also contributes to unnecessary direct and indirect health costs. (27) It is estimated that one in five medicines commonly used in older adults in primary care may be inappropriate. (28, 29)

Although the harm associated with polypharmacy in observational studies supports the need for deprescribing, there is a dearth of direct evidence demonstrating the long-term safety and effectiveness of deprescribing. Two recently published systematic reviews of deprescribing studies showed no-effect (30) or a potentially beneficial effect (31) on mortality of deprescribing interventions. The 2016 systematic review by Page *et al* found mortality was significantly reduced in randomised studies in which patient-specific interventions to deprescribe one or more medicines in older adults were applied. (31) The 2016 systematic review and meta-analysis by Johansson *et al*, however, found no effect of complex interventions to reduce polypharmacy or mortality, rates of hospital admissions or the number of medications used. (30) This implies that more effective strategies to reduce

potentially inappropriate polypharmacy need to be developed and tested in large-scale, pragmatic, controlled trials. Equally, there is need to elicit and evaluate outcomes that matter to patients so that interventions can be designed to improve these outcomes.

1.2 Setting for this study

Most Australians receive primary health care through their GP who also acts as a coordinator and gatekeeper for government-subsidised specialist and allied health services. (32) Consequently, GPs and the primary health care setting are routinely targeted in major health initiatives to improve population health. (33) Primary health care in Australia encompasses a large range of providers and services across the public, private and non-government sectors. General practice is partially funded under Medicare, predominantly through a 'fee-for-service' model, whereby GPs receive government remuneration for individual patient consultations and treatments thereby offsetting the out-of-pocket cost for the patient. Bulk-billing is where a practice directly bills Medicare for a health service and does not charge the patient an out-of-pocket fee. Under the National Health Reform Agreement, strengthening GP and primary health care services has been identified as a critical step towards ensuring the effectiveness and efficiency of the Australian health system. (34) General practitioners are therefore arguably the most important agents in improving the care for patients in the community. This includes ensuring the Quality Use of Medicines (QUM), defined under the National Medicines Policy as the safe, judicious, effective and cost-effective use of medicines in all Australians. (35)

Consultant pharmacists (CPs), who are accredited to undertake medication reviews, also have an important role in enhancing QUM in Australia. Consultant pharmacists are reimbursed by government to undertake comprehensive medication reviews in the patients' place of residence on referral from their GP. For individuals residing in the community, this service is known as a Home Medicines Review (HMR), which is funded by government through the Sixth Community Pharmacy Guild Government agreement. (36) There is currently support for greater involvement and integration of pharmacists into general practices in Australia, as is the case in the United Kingdom (UK), United States (US) and Canada, to improve QUM and outcomes of patients with chronic disease. (37, 38)

Effecting any clinician-led behaviour change in primary care, including facilitating GP-led deprescribing in older people, is difficult and requires complex, or multifaceted, intervention. (39) Factors influencing the use and prescription of one or more PIMs in

older people are broad and multi-dimensional. The likelihood of successful implementation of a complex intervention is increased when the 'implementers' have been engaged in eliciting, understanding and addressing barriers and enablers to change in a particular context and using those insights in designing the intervention. (40) Consequently, this study sought to develop and pilot a multifaceted GP-led intervention to minimise potentially inappropriate polypharmacy in community living older people, addressing GP and CP barriers and enablers to deprescribing in primary care in Australia.

A mixed methods approach was used to address the research problem for this study with pragmatism being the paradigm applied to the investigation, given the potential application of these research findings to real-world practice. (41, 42) The three specific aims of the study, which aligned with three specific study phases were:

- Phase 1 – To investigate prescribers' perspectives on factors which shape their behaviour towards continuing or discontinuing PIMs in adults
- Phase 2 – To explore the views of a sample of general practitioners and consultant pharmacists about potentially inappropriate polypharmacy and the reasoning they apply to deprescribing in older people in primary care, including factors that influence this process
- Phase 3 – To evaluate the feasibility, effectiveness and safety of a multifaceted GP-led intervention in community living older people in primary care, which was developed using the findings from Phases 1 and 2.

Many deprescribing intervention studies to date have been led by clinicians who do not have an ongoing therapeutic relationship with, and tacit knowledge of, the patient and have occurred in the hospital or residential aged care setting. This research addresses this shortcoming and will contribute to knowledge regarding strategies to facilitate GP-led deprescribing with their community living older patients in the Australian primary care setting. The developmental qualitative work will provide a greater understanding of clinicians' perspectives of potentially inappropriate polypharmacy and factors that inhibit or facilitate deprescribing. The use of mixed methods in the exploratory study will allow critical components of a successful intervention to be identified for future application in clinical practice, or, if the intervention is unsuccessful, whether this was the consequence of implementation failure or genuine ineffectiveness of the intervention, learnings from which can be applied to future studies. Importantly, the qualitative evaluation of the exploratory study will highlight perceived value, if any, from the GPs' and patients' perspective, which may assist in identifying meaningful measures and outcomes to inform future deprescribing studies and policy decisions.

1.3 Overview of thesis structure

This thesis comprises nine chapters. This first chapter provides an overview of the research problem and context, and presents the thesis aims and structure. Chapter 2 is a comprehensive review of current literature pertaining to the potential harms from polypharmacy, the need for deprescribing and the way in which this study intends to contribute to the body of knowledge in this important and emerging field of research. In Chapter 3, the research approach used in this three-phased mixed methods study will be described, including the research paradigm applied to the investigation and research design. Chapter 4 presents the methods and findings of the systematic review and thematic synthesis of available literature of prescribers' perceived barriers and enablers to minimising potentially inappropriate medicines (PIMs) chronically prescribed in adults. Recognising the importance of context to the success or failure of complex interventions, Chapter 5 presents the methods and findings of a qualitative investigation involving a sample of South-East Queensland GPs and CPs caring for older people with polypharmacy still residing in the community. Their views were sought regarding potentially inappropriate polypharmacy, the reasoning they apply to deprescribing in primary care as well as factors that support or inhibit this cognitive process. Findings from Chapter 4 and 5 were subsequently used to inform the design of a multifaceted deprescribing intervention. Detailed methods for this exploratory, mixed methods study are presented in Chapter 6. Quantitative results and qualitative findings of the exploratory study are presented in Chapters 7 and 8, respectively. Chapters 4, 5, 7 and 8 all provide a discussion at the end of each chapter, stating the strengths and limitations of the relevant investigations for each phase of the study, comparison of findings to existing literature, and new insights from the research. The final chapter, Chapter 9, is a synthesis and interpretation of the all three phases of the investigation, including the significance of the research findings and potential implications for practice, policy and future research.

Chapter 2 Literature review

This chapter provides an overview of the research literature on polypharmacy, deprescribing and behaviour change interventions influencing primary care physicians' practice, including prescribing decisions. Specifically, the objectives of this chapter are to: 1) provide definitions of common terms used in this thesis to ensure a mutual understanding of essential nomenclature; 2) outline the prevalence and evidence of harm from polypharmacy and potentially inappropriate medication (PIM) use; 3) appraise the evidence of the safety and efficacy of deprescribing interventions and interventions to change clinicians' behaviour in primary care and; 4) highlight areas where further research is required and how this study will contribute to the knowledge in this field. In identifying relevant literature for this chapter, keyword searches of PubMed, Scopus, Google Scholar, the University of Queensland library website and the candidate's personal reference library were undertaken throughout the period of candidature and up until November 2017. Formal search strategies were augmented by snowballing techniques (i.e. identifying relevant papers from reference lists of pertinent articles) and notification by colleagues of newly published articles.

2.1 Definitions

2.1.1 Polypharmacy, potentially inappropriate medicines and potentially inappropriate prescribing

Polypharmacy has been defined in two ways in the literature: the concomitant use of multiple drugs as measured by a simple count of medications or; the use of more medications than are clinically indicated which considers the appropriateness of each therapy. (43) The bulk of the literature looking at the epidemiology and consequences of 'polypharmacy' has employed the first definition that uses medication counts and thresholds for harm. (24)

For the first definition of polypharmacy centred on 'many medicines', there is no consensus regarding the number of medications that constitutes polypharmacy, (44) although a threshold of five or more medicines is commonly used for 'polypharmacy' and ten or more medicines for 'hyperpolypharmacy'. (45, 46) It is important to note that the concurrent use of multiple medicines may be entirely appropriate, especially in individuals with multimorbidity. (47, 48) Therefore, the term 'potentially inappropriate polypharmacy' has been used to distinguish polypharmacy in which one or more medicines are possibly inappropriate when multiple regular medicines are used concurrently. (3) As asserted by

Aronson, to ascertain whether polypharmacy is or is not appropriate, each medicine must be considered individually, in the context of the person for whom it is prescribed, as well as in the context of the whole prescription. (47) A 'potentially inappropriate medicine' (PIM) has been defined as that in which the actual or potential harms of medication therapy outweigh the actual or potential benefits. (49) The addition of the term 'potentially' when discussing either polypharmacy or single medicines is important, especially in older people, where there is a lack of strong clinical evidence on the risks and benefits of medicines. Often, it is not until reduction or withdrawal of therapy is attempted that it becomes clear if continuing therapy is in fact necessary and appropriate in an individual. (50)

The term 'potentially inappropriate prescribing' or PIP, however, is far more encompassing. The definition includes not only the overuse, but also misuse and under-use of medicines (i.e. fewer medicines than are clinically indicated). (49, 51) Under-prescribing has emerged as a matter of concern in older people with polypharmacy in more recent times, but there is evidence that under-prescribing and polypharmacy often coexist. (52) (53) In one study of 150 older people, among participants receiving five or more medicines, 42.9% were under-treated, compared to 13.5% of those using four or fewer medicines (odds ratio [OR] 4.8, 95% Confidence Interval [CI] 2.0 to 11.2). (54) One explanation of this finding is the unwillingness of doctors to prescribe additional medicines for patients with polypharmacy due to concerns around regimen complexity, fear of adverse events or interactions and poor adherence. (54)

Under-prescribing as a component of PIP will not be examined as part of this thesis. Although under-prescribing is acknowledged as an important issue, it is hypothesised that minimising potentially inappropriate polypharmacy may provide an entry point for more appropriate prescribing generally, including the initiation of essential medicines in older people with polypharmacy.

Throughout this thesis, 'polypharmacy' refers to the use of multiple medicines concurrently (usually five or more regular medicines, unless otherwise stated). If there is reference to one or more medicines being potentially inappropriate, the terms PIM or potentially inappropriate polypharmacy will be used. The terms medicine/s, medication/s and drug/s have also been used interchangeably throughout this thesis.

2.2 Prevalence of, and outcomes associated with, polypharmacy and PIMs in community living older people

2.2.1 Prevalence and trends in polypharmacy

Polypharmacy can occur at any age, but it is older people who continue to be the greatest users of medicines and who experience a disproportionate number of medication-related events or harm. Studies in the United States and Australia indicate at least one in two older people (aged 65 years or greater) living in the community use five or more prescription, over-the-counter or complementary medicines every day, and the number used increases with age. (16, 55) The percentage of older people in the community using ten or more medications has been estimated to be between 5 and 26%, with higher rates again reported in residential aged care. (16, 46, 56)

The prevalence of polypharmacy is also increasing over time. A nationally representative survey of trends in prescription drug use among 37,959 non-institutionalised US adults aged 20 years and older from 1999-2012 found that the prevalence of polypharmacy (i.e. ≥ 5 prescription drugs) increased, across all age groups (estimated prevalence 8.2% in 1999-2000 to 15% in 2011-2012; difference 6.6%, 95% CI, 4.4%-8.2%; p for trend <0.001). The highest prevalence of polypharmacy was in people aged ≥ 65 years (39% in 2011-2012, 95% CI 35-44%). (57)

Similarly, a large repeated cross-sectional study of pharmacy claims data in Ireland from 1997 to 2012 (range 338,025 – 539,752 individuals), found that the prevalence of polypharmacy (i.e. ≥ 5 prescription drugs) increased, particularly among older individuals (from 17.8% to 60.4% in those aged ≥65 years). The adjusted incidence rate ratio (IRR) for polypharmacy in 2012 compared to 1997 was 4.16 (95% CI 3.23 to 5.36), and for excessive polypharmacy (defined as ≥ 10 regular medicines) it was 10.53 (95% CI 8.58 to 12.91). (58)

Whilst a directly comparable, current Australian study is not available, figures from the Pharmaceutical Benefits Scheme (PBS) showed the number of prescriptions in Australia rose from 179 million in 1997 to more than 288 million in 2014. (59) This implies trends in Australia may be broadly consistent with those reported internationally. Polypharmacy is therefore the paradigm for modern prescribing. (60)

2.2.2 Drivers of polypharmacy

Key drivers of polypharmacy are the ageing population, rising tide of multimorbidity and plethora of disease-specific, evidence-based guidelines for the management of long-term conditions. (48) Australian general practice data from 2015-2016 indicates that 57% of people aged 65 years and older have three or more chronic conditions and almost 10% had seven or more chronic conditions. (15) This is consistent with international data. A cross-sectional study in the UK in which data were extracted from the primary care electronic health records of 1.75 million people indicated that 64.9% of people aged 65-84 years and 81.5% of people aged ≥85 years were classified as having multimorbidity (defined in their study as two or more chronic conditions concurrently). (61)

Disease-specific guidelines rarely account for managing patients with multimorbidity and so, the application of multiple disease-specific guidelines by clinicians to a patient with a number of chronic conditions, increases the likelihood of potentially inappropriate polypharmacy. (14) This can be exacerbated by guideline-derived quality indicators and performance incentives at the health system level. (62)

There are a range of other drivers of polypharmacy including a lack of knowledge of geriatric pharmacology and exclusion of older multimorbid patients from clinical trials. Patient or carer expectations regarding health and medicines and a focus on pharmacological versus non-pharmacological therapies can also drive polypharmacy.(20) At the provider level, intervening to withdraw a chronically-prescribed medication can be a difficult and time-consuming task in this patient group. In time-pressured, routine care environments, there is often a focus on the management of acute illness, rather than proactive management of chronic disease. (63) It can be challenging for clinicians to identify adverse drug events (ADEs), and their misinterpretation as new disease, may invoke the addition of more medicines. (63) Fear of precipitating disease relapse or drug withdrawal syndromes and prescriber sensitivity to accusations of ageist discrimination if not prescribing more drugs can further undermine proactive attempts to minimise PIMs.(20) The provider is also faced with a range of health system drivers of polypharmacy such as the involvement of multiple specialist prescribers across different care settings who again take a disease-specific, rather than coordinated, whole-patient approach to care. (64) Prior to the publication of the systematic review of factors which shape prescribers' behaviour towards continuing or discontinuing PIMs in adults published

in 2014 as part of this thesis, syntheses of literature on drivers of polypharmacy at the provider level were lacking. (9)

2.2.3 Harms from polypharmacy

The use of multiple concurrent medications has been associated with poor health outcomes in single observational studies, but a systematic review of adverse health outcomes associated with polypharmacy in community dwelling older adults published in 2014 by Fried *et al* found mixed results. (44) However, no minimum threshold number of medications was specified to define polypharmacy. The authors were particularly interested in examining the relationship between the number of medications prescribed and patient outcomes regardless of the appropriateness of each medication. A total of 50 observational studies were included in the review, but due to marked heterogeneity among studies regarding their definition of polypharmacy and the outcomes studied, no attempt was made to combine the results. Studies were rated for their adjustment of comorbidity, a significant confounder between the relationship of polypharmacy and outcomes, and the majority of studies were rated as 'good' in this regard. Some studies demonstrated an association of polypharmacy with falls, related risk factors and injury, ADEs, adverse symptoms, decline in physical and cognitive function, hospitalisation and mortality, while other studies failed to find these associations. Three studies examined multiple categories of a number of medications and did not find associations between three or fewer medications versus no medications and the outcome of interest, but did find associations for categories including a higher number of medications. (65-67) The reviews' authors expected that studies with less adjustment for comorbidity would be more likely to demonstrate an association between polypharmacy and adverse outcomes because they hypothesised that polypharmacy was predominantly a marker of patients' underlying health status. This was not clearly shown though and the authors concluded that this indicates the multifactorial nature of the outcomes examined in the included studies. A key difficulty in interpreting this review was the lack of a minimum threshold of medicines constituting polypharmacy.

An Australian study of 1,705 community dwelling older men aged 70 years attempted to identify medication thresholds associated with medication-related adverse effects. After adjusting for age and number of comorbidities, the study found that a threshold of five or more medications was associated with medication related adverse effects for frailty, disability, mortality, and falls. (68) Specifically, the number of concomitant medications

was 6.5, 5.5, 4.5, and 4.5 medicines in association with frailty, disability, mortality, and falls, respectively, and the association strengthened with each additional medication. That is, for each one medicine increase in the number of medicines, the adjusted odds ratios (AORs) were 1.13 (95% CI 1.06 to 1.21) for frailty, 1.08 (95% CI 1.00 to 1.15) for disability, 1.09 (95% CI 1.04 to1.15) for mortality, and 1.07 (95% CI 1.03 to 1.12) for incident falls. Although this study was limited by its ability to adjust for the severity of comorbidities, it lends support to the threshold of five or more medications as being appropriate for the definition of polypharmacy. (69)

A large study from Payne *et al* (70), published after the 2014 systematic review by Fried *et al*, again attempted to adjust for the degree of comorbid conditions on the association between polypharmacy and adverse outcomes. They reported the findings of a retrospective cohort analysis using linked electronic health records from primary and secondary care for 180,815 Scottish adults with long-term conditions and taking multiple medicines. In the study, authors modelled the association of polypharmacy with unplanned admission for patients, but used an interaction term in their multiple logistic regression modelling to adjust for the different numbers of long-term conditions. The authors found that unplanned hospitalisation was strongly and consistently associated with the number of regular medications prescribed (OR 1.25, 95%CI 1.11 to 1.42 for four to six medications and OR 3.42, 95% CI 2.72 to 4.28 for ≥10 medications, compared to one to three medications, respectively). However, this effect was greatly reduced for individuals with multiple chronic conditions. In patients with six or more conditions, those on four to six medications were no more likely to have unplanned admissions that those with fewer than three medications (OR 1.00, 95% CI 0.88 to 1.14). The use of ≥ 10 medications remained consistently associated with an increased risk of unplanned hospitalisation, regardless of the number of comorbidities, although the size of the effect was reduced in those with four to six comorbidities (OR 1.50, 95% CI 1.31 to 1.71). The median age of study participants was 49 years (36-63 years). The authors repeated their analysis restricting age to those 65 years and older though, and found very similar results.(71) This study's findings indicate the importance of considering polypharmacy in the clinical context for which medications are being prescribed. The attenuation in strength of association between polypharmacy and unplanned hospital admission with increasing number of comorbidities suggests the use of multiple medicines is not necessarily harmful and therefore inappropriate.

Several conclusions can be drawn from the aforementioned observational studies. The concurrent use of multiple medicines is associated with harm in many situations, but not always. Polypharmacy may therefore be entirely appropriate, especially in individuals with multimorbidity. Evidence suggests that four to five or more concurrently used medicines appears the threshold at which there is an association with many adverse outcomes. However, given that thresholds vary depending upon the outcome of interest, it would seem that more sophisticated alternatives, which consider the appropriateness of therapy in the context of individuals and all their clinical circumstances, may be of greater value in predicting or determining patient harm from polypharmacy. (71) Randomised controlled trials, which could mitigate confounding due to the complex relationship between medication regimens and comorbidities, may be required to definitively answer the question of attributing outcomes to polypharmacy. (44) Until better risk-adjusted predictive tools for medication-related outcomes become available, polypharmacy, defined by medication number alone, appears a useful proxy of potential medication-related harm, especially in older people.

2.2.4 Polypharmacy and PIMs

Polypharmacy is also an indicator of PIP and PIM use. (26) This is based on the finding that the number of medicines prescribed is the single most important predictor of the presence of one or more inappropriate medicines. (1, 2) There are multiple tools that attempt to identify PIMs. These tools are either explicit (based on predetermined criteria or standards) or implicit (requiring the clinical judgment of the assessor). (72)

Explicit criteria are usually developed from reviews of published evidence and, in the absence of evidence, expert opinion and consensus. Explicit criteria are generally drug- or disease-orientated and can be applied with little to no clinical judgement. (49) They are therefore useful to apply at a population level to identify, for example, the prevalence of PIMs from prescribing databases. The usefulness of explicit criteria is more limited at an individual level however, because they may not account for factors consistent with high-quality, individualised care, such as levels of comorbidity and patient preferences. (49) In other words, they do not encompass the clinical context in which decisions are made. (73) Other key limitations include low physician acceptability due to the perception that explicit criteria limit freedom to prescribe (74), and that consensus approaches from which explicit criteria are often derived have little evidence of validity and reliability. (49) Examples of explicit tools identifying PIMs from multiple medicine and therapeutic classes include the

Beers (75), PRISCUS (German abbreviation) (76), McLeod (77), 'Improved Prescribing in the Elderly' (IPET) (78), 'Fit for The Aged' (FORTA) (79), and 'Screening Tool to Alert doctors to Right Treatments' (STOPP) criteria. (80)

The Medication Appropriateness Index (MAI) appears to be the most widely utilised implicit tool, but its use is time consuming and so is generally restricted to the research setting. (49) It rates ten elements of prescribing: indication, effectiveness, dose, correct directions, practical directions, drug–drug and drug–disease interactions, duplication, duration and cost. The standardised rating process generates a weighted score of overall prescribing appropriateness. The tool demonstrates good reliability and content validity, although its utility is limited by potential floor effects, such that the number of 'inappropriateness' ratings tends to be low. (81)

2.2.5 Prevalence and trends in PIMs

The reported prevalence of PIMs may vary depending upon the tools or criteria being used to measure prescribing appropriateness. A systematic review of 19 studies (7 from the US and 10 from countries in Europe and Asia), estimated that one in five prescriptions in primary care for individuals >65 years was inappropriate. (28) Fourteen of these studies used the Beers criteria to determine appropriateness. A more recently published systematic review of 52 studies conducted in Europe estimated the overall prevalence of potentially inappropriate prescribing in community dwelling older people was 22.6% (95% CI 19.2 to 26.7%), although this study also considered examples of under-prescribing in the assessment of PIP. (82)

A large Australian cohort study involving 192,363 veterans 70 years and older found that approximately 20% of this population were taking one or more PIMs, as defined by Beers or McLeod criteria. This suggests that the prevalence of PIM use in Australia appears broadly consistent with international data. (29) Higher rates again have been reported in residential aged care facilities (RACFs) with up to one in two older Australians taking at least one PIM, (83, 84) which is again broadly consistent with international data. (85)

Only one study could be found which reported contemporary data regarding trends in the prevalence of PIM use. It was the previously mentioned large repeated cross-sectional study of pharmacy claims data in Ireland from 1997 to 2012 (range 338,025 – 539,752 individuals) which found the prevalence of PIM use (as defined by the STOPP criteria) rose from 32.6% in 1997 to 37.3% in 2012, but the odds of having any PIM were lower in

2012 compared to 1997, after adjusting for gender and the number of medicines (OR 0.39 CI 0.39-0.4). In considering specific examples of PIM use, the authors found that some examples of PIM use had decreased over time (e.g. high dose aspirin and digoxin) whilst others had substantially increased (e.g. long-term proton pump inhibitors at maximal dose increased from 0.8% to 23.8%). (58) It is difficult to extrapolate these findings to trends in PIMs use in other countries, including Australia. It does however confirm that, whilst rates of prescribing of PIMs remain high, patterns of prescribing change over time, such that PIMs that were once commonly prescribed may reduce over time, with other new examples emerging. The usefulness of explicit criteria to identify PIMs is therefore time-sensitive, meaning the criteria must be updated regularly so they do not become redundant. In contrast, structured decision guides or frameworks, (86) which provide prescribers with a systematic approach to reviewing an individual's medicines are not time-sensitive, as they require a consideration of current evidence of appropriateness of medications.

2.2.6 Harms from PIMs

Observational studies have shown that PIM use is independently associated with a range of adverse health outcomes in community living older people including ADEs, hospital presentations and poorer health-related quality of life. (22, 87) In older people in residential care, individuals who begin use of a PIM in the previous year are at a higher risk of hospitalisation and dying compared to non-PIM users. (23) This was shown in a retrospective claims database analysis of 7,594 elderly nursing home residents in Indiana (mean age, 83.07 years). Incident PIM users were more likely to be hospitalised (OR 1.27, 95% CI 1.10 to 1.46) and more likely to die (OR 1.46, 95% CI 1.31 to 1.62) in the 12 months after first receiving a PIM than non-users, after adjusting for demographic and clinical risk factors. (23)

A retrospective cohort study of 174,275 insured persons 65 years and older in the US looked at the ability of three different explicit criteria (2003 and 2012 Beers, and the 2008 STOPP criteria) to predict ADEs, hospitalisations and emergency department (ED) visits. (87) The data source was managed care administrative claims from 2006-2009 and mean follow-up period of the cohort was approximately two years. The prevalence of inappropriate prescribing was 34.1%, 32.2%, and 27.6% for the 2012 Beers, 2003 Beers, and the STOPP Criteria, respectively. Exposure to a PIM according to any of these criteria was strongly associated with an increased risk of ADEs, Emergency Department (ED)

visits, and hospitalisations in both unadjusted and adjusted models. In the primary unadjusted model, PIM exposure was associated with a 2- to 3-fold increased risk across all outcomes for the 2003 Beers, 2012 Beers, and STOPP Criteria. The relationship between PIM exposure with all of criteria and each of the three outcomes was stronger (HRs: 3.67 – 5.30) in the time varying models in which exposure and outcome were assessed in the same month. Not all adverse outcomes examined could be attributed to the presence of PIMs however, highlighting the need to combine these criteria with clinical judgement.

A retrospective cohort study by Cahir *et al* of 931 community dwelling patients aged ≥ 70 in Ireland evaluated the prevalence of, and harms from, PIMs according to the 2008 STOPP criteria. (22) Forty-two percent of patients had one or more PIMs, which is slightly higher than the prevalence reported in other community living older people in the aforementioned systematic reviews. (28, 82) After adjusting for covariates, the study found that patients with two or more PIMs were twice as likely to have an ADE (AOR 2.21, 95% CI 1.02 to 4.83, $p < 0.05$), have significantly lower quality of life ($p < 0.001$) and nearly a two-fold increased risk in the rate of accident and emergency visits (adjusted IRR 1.85, 95% CI 1.32 to 2.58, $p < 0.001$). (22)

It is clear the presence of PIMs as determined by explicit criteria is associated with significant adverse outcomes, contributing to considerable direct and indirect health costs, although this cost is yet to be quantified in the Australian context. Lists of PIMs such as Beers and STOPP criteria comprise medicines whose benefits are outweighed by harms in most circumstances, e.g. non-steroidal anti-inflammatory drugs, anticholinergic agents and benzodiazepines. (63) In the Australian context, these drugs account for relatively few ADEs, reinforcing the point that these criteria may only predict a fraction of medication-related adverse outcomes. (88) Furthermore, whilst such criteria may be of use at a population level to gauge medication appropriateness, their utility at an individual patient level is limited for two key reasons: their inability to fully account for the clinical context in which medicines are being used; and failure to identify other medicines not appearing in such lists which may be associated with significant potential for harm in an individual patient. The process of identifying medicines as potentially inappropriate in an individual patient is therefore more complex than simply applying a standardised list of ‘drugs to avoid’. Several decision guides or frameworks that have been developed to support the

process of identifying and discontinuing or deprescribing one or more PIMs and these will be discussed in 2.3.4, ‘Structured guides to assist deprescribing’.

Thus far, it has been established that polypharmacy is associated with patient harm in many, but not all instances. The number of medicines used is also the single most important predictor of the presence of one or more PIMs, which is also independently associated with adverse outcomes. Therefore, polypharmacy, defined by medication number alone, appears a useful proxy of potential medicine-related harm, especially in older people. In the next section, the definition and current evidence on the efficacy and safety of deprescribing will be examined.

2.3 Deprescribing

2.3.1 Definition of deprescribing

The term deprescribing first entered the medical lexicon in 2003 (89) and embodied a response to the harms of polypharmacy and PIMs. However, no single definition for deprescribing exists in the medical literature. One of the most comprehensive definitions offered to date is that by Scott *et al*, page 827, which defines deprescribing as, “the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient’s care goals, current level of functioning, life expectancy, values, and preferences.” Reeve *et al* also states that two of the essential characteristics of a definition of deprescribing are that medications to be ceased are inappropriate and that deprescribing is supervised by a health care professional, so that deprescribing is distinguished from what it is not (i.e. patient non-adherence or prescribers denying effective treatment). (90) However, as identified by Reeve herself, it may be almost impossible to identify *a priori* medicines that are unequivocally inappropriate as it is often not until discontinuation is attempted and the individual is followed-up that the actual benefit (or harm) of a medicine in an individual becomes apparent. (50)

There is also debate regarding whether dose reduction, as opposed to complete discontinuation, should be included in the definition. For example, Reeve also states that, although controversial, deprescribing should only refer to medication withdrawal, not reduction, on the basis that if a medication truly is inappropriate, it should be ceased completely. (90) However, it is important to acknowledge that deprescribing sits on the spectrum of ‘good prescribing’, spanning therapy initiation, dose titration, changing or adding medicines, and switching, reducing or ceasing medicines. (3) This raises

questions as to whether Reeve's purist definition is anchored in the reality of clinical practice. There may be instances in which a reduction in dosing rather than complete cessation of a medicine meets the definition of deprescribing (e.g. changing a regular dose to as required [prn] benzodiazepine or proton pump inhibitor use). (91)

The concept of stopping or reducing medicines is well known to clinicians and is documented in the World Health Organisation's (WHO) *Guide to Good Prescribing*. (92) Furthermore, deprescribing embodies Quality Use of Medicines (QUM) principles (i.e. the safe, judicious, effective and cost-effective use of medicines) as outlined in Australia's National Medicines Policy which was first launched in December 1999. (35) Reviewing and discontinuing therapy also features in Australia's National Prescribing Services' Prescribing Competencies, which aim to guide Australian prescribers to put QUM into practice. (5)

Like other interventions such as initiating a medication, deprescribing is a positive, affirmative action that carries potential harms and benefits and requires informed consent, adherence and monitoring. (3) It has been suggested by clinicians and researchers that deprescribing be considered whenever there is polypharmacy, suspected or probable adverse medication effects, a lack of efficacy or absence of a clear indication for a medicine, or there has been a change in patient care goals or health trajectory. (50, 93)

2.3.2 Deprescribing interventions targeting multiple medication classes (polypharmacy)

A vast number of studies spanning several decades have examined the effect of interventions to improve or optimise prescribing broadly, which directly or indirectly encompassed attempts to reduce the number of medicines prescribed or the prevalence of PIMs. In other words, these studies may have included deprescribing, or elements of it, but they were not specifically focussed on deprescribing. For example, three previous Cochrane Reviews reported on interventions to optimise prescribing in older patients in the community, (94) care homes, (95) and hospitals. (96) Interventions included multi-disciplinary case-conferencing, education for patients and clinicians, computerised decision support, information transfer and pharmacist-mediated medication reviews or a combination of these elements. Medication reviews by a pharmacist may have involved support from a specialist and/or the use of criteria based processes (e.g. application of the MAI or STOPP/START criteria). (94-96) These interventions demonstrated improvements in prescribing (such as improvements in MAI score or a reduction in medicines listed as

inappropriate based on explicit criteria) but their effects on clinical outcomes, such as ADEs, quality of life, hospitalisations, morbidity and mortality have been mixed. Comparatively fewer studies have focused exclusively on deprescribing, although published research in this area has increased in the last ten years.

The goal of deprescribing is to minimise potentially inappropriate polypharmacy and improve outcomes, (63) but long-term efficacy and safety data derived from controlled trials are lacking. Evidence to date suggests short-term efficacy and/or a lack of harm from withdrawing medicines from a single therapeutic category in people 65 years and older, such as antihypertensive, benzodiazepine and psychotropic agents. (97)

Evaluation of the limited evidence to date on the impacts of deprescribing interventions targeting multiple medicines has shown little to no beneficial impact regarding 'clinically meaningful outcomes'. A 2016 systematic review and meta-analysis examined the effects of strategies to reduce polypharmacy on mortality, hospitalisation and number of changed medicines. (30) Studies were limited to those selecting patients 65 years or older taking four or more medicines, and without terminal illness. A total of 25 studies (21 randomised controlled trials, four non-randomised controlled studies) including 10,980 participants, across all health settings were in included in the analysis. Only five of the 25 studies explicitly aimed to reduce the quantity (dose or number) of medicines, with the remaining studies aiming to improve the appropriateness of the medication regimen by removing, where possible, inappropriate medicines. Interventions were complex and targeted polypharmacy or multiple drug classes (rather than a single drug class) but common to all interventions was a process of medication review. Thirteen studies reported on pharmacist-led interventions, eight on multidisciplinary team-led interventions and four on physician-led interventions. Studies used a variety of methods to support the medication review process, including: appropriateness criteria (e.g. MAI); lists of drug interactions; and reconciliation methods and expert opinion. All of these methods may have been supported by a range of electronic or non-electronic strategies (e.g. clinical decision support, reminders). Fifteen studies were conducted in primary care, seven in nursing homes and three in hospital. The duration of study follow-up ranged from six weeks to 18 months and studies were conducted in developed countries in Europe, in the UK, USA, Canada and Australia.

Meta-analysis of eighteen studies reporting on all-cause mortality showed no effect in favour of intervention (OR 1.02, 95% CI 0.84 to 1.23). Although statistical heterogeneity

was low (I^2 = 8%; p = 0.362) in regard to effect measures, there was a high degree of methodological heterogeneity regarding study design. Study results were unable to be pooled for the outcomes of hospitalisation, but authors noted that only two of eleven studies reported reductions in hospital admissions in favour of intervention. For changes in the number of drugs taken, the authors noted that, at baseline, patients were taking on average 7.4 medicines in both the intervention and the control groups. The weighted mean number of drugs at follow-up was reduced (-0.2) in the intervention group, but increased (+0.2) in control group. Whether these results were statistically significant could not be determined as most studies did not report standard deviations.

There are some key strengths and limitations to this review. Importantly, this review only considered 'clinically relevant endpoints' (mortality and hospitalisation) as opposed to previous reviews of prescribing interventions which focused on surrogate parameters such as medication appropriateness assessed by the application of implicit or explicit criteria. It also evaluated change in numbers of drugs taken which is important given the association between the number of medicines and ADEs seen in observational studies. The authors attempted to account for the clinical and methodological heterogeneity of included studies by only pooling those for which there was sufficient homogeneity to do so and applying random effects to the meta-analysis regardless of the degree of statistical heterogeneity. The follow-up in included studies was short (range six weeks to 18 months) for the outcome of mortality, and so questions remain regarding the long-term impact of deprescribing on mortality. A key challenge in conducting this review was the absence of clear and comprehensive descriptions of study methods and the authors stated that future intervention studies should take greater care in reporting these. The authors concluded that the evidence of effectiveness of interventions to reduce polypharmacy is very limited. They cautioned that, given the quality of existing evidence was categorised as low to very low, any estimates of effect should be deemed highly uncertain, owing to imprecise results due to small numbers of outcome events and wide confidence intervals. The authors identified an ongoing need to develop effective complex interventions for testing in large-scale RCTs.

The difficulty in generalising the results of this review to a GP-led intervention in primary care is that, in all but one study set in a nursing home, the clinician conducting the medication review was not the physician primarily responsible for the patient's care. (98) Furthermore, only a minority of interventions appeared to actively involve patients in the

review process (e.g. through education) or, if they did, study authors failed to report this. Therefore, the impact on mortality and hospitalisations of a medication review, conducted by a GP upskilled in deprescribing, who has an ongoing therapeutic relationship with their patient, requires further investigation.

A second systematic review and meta-analysis published in 2016 examined the feasibility and effect of deprescribing in older adults on mortality and health. (31) Unlike the previously described review, the authors included experimental and observational deprescribing studies targeting one or more prescription medications or classes of medications in older people. One hundred and thirty-two studies, including 34,143 participants aged 73.8 ± 5.4 years, across all health settings, met the inclusion criteria. The majority of studies investigated the withdrawal of a single medication, class of medications (e.g. beta blockers) or therapeutic category (e.g. antihypertensive agents). All but four studies were conducted in nations throughout Europe and in the UK, USA, Canada, Australia and New Zealand. Interventions were categorised as patient-specific (i.e. where one or more target medications were flagged for deprescribing through processes such as medication review or clinical decision support) or educational (where educational sessions were delivered to clinicians to modify prescribing behaviour). Studies with palliative, terminal or moribund patients were excluded. The primary outcome measure was mortality, but a range of secondary outcomes measures were also investigated.

Twenty-one studies included in the review investigated deprescribing polypharmacy. Of the interventions investigated, 18 were ‘patient-specific’ and three were ‘educational’ interventions. Eleven of the 18 patient-specific interventions (e.g. involving medication reconciliation or review) were physician-led, (99-109) with the rest led by pharmacists or nurses. In none of these 11 studies was the intervention delivered by the patient’s usual treating GP or physician, either because the physician was the investigator and/or because the study occurred in the hospital setting. The three educational interventions did target the patient’s usual care team (including the doctor in two studies) but all three occurred in a residential aged care setting.

Of the twenty-one studies which looked at deprescribing polypharmacy, ten randomised trials (four each in primary and residential care, two in hospital) reported on mortality but pooling these study findings found no statistically significant effect on mortality (OR 0.82, 95% CI 0.61 to 1.11; participants = 3,151; studies = 10; follow-up duration; weighted mean

(SD) of 9.6 ± 3.9 months). However, when a sub-group analysis was conducted assessing mortality according to type of intervention, patient-specific interventions significantly reduced mortality (OR 0.62, 95% CI 0.43–0.88; participants = 1906; studies = 8), whereas generalised educational programmes did not (OR 1.21, 95% CI 0.86–1.69; participants = 1245; studies = 2). The authors concluded that patient-specific, individualised deprescribing approaches are needed in older adults.

In the same review, deprescribing was also not associated with a statistically significant change in adverse drug withdrawal events, incidence of ADEs, or changes in cognitive function or quality of life using standardised measures. Deprescribing to reduce polypharmacy did not significantly reduce the risk of experiencing single falls (OR 0.65, 95% CI 0.40 to 1.05; participants = 2,173; studies = 5), although, those who did fall had significantly fewer falls overall in the intervention compared to control group (Mean Difference [MD] -0.11, 95% CI -0.21 to -0.02; participants = 844; studies = 3).

A key limitation of this systematic review was the methodological heterogeneity of studies, compounded by very broad inclusion criteria. The follow-up durations (which were usually short), health care setting, age and health status of participants were highly variable, and most studies demonstrated uncertain or high risk of bias. A further limitation of this review was the high number of sub-analyses which were not specified *a priori*, (110) increasing the potential for spurious statistically significant associations.

Considering these two reviews, it appears deprescribing interventions to minimise potentially inappropriate polypharmacy have little to no impact on clinically meaningful endpoints, except for patient-specific interventions in older patients. However, the studies included in these reviews have been implemented primarily by investigators or hospital clinicians where tacit knowledge of the patient or an ongoing therapeutic relationship between prescriber and patient are lacking. In the next section, studies investigating GP-led interventions to deprescribe multiple medicines will be considered.

2.3.3 GP-led deprescribing interventions in community living older people

The foregoing discussion raises an important question: could primary care physicians, who have tacit knowledge of, and an ongoing therapeutic relationship with their patients, realise better medication-related outcomes if they were to be upskilled in the practice of deprescribing? This question is yet to be examined in the Australian healthcare context.

Most studies targeting GPs caring for community living older people have investigated the effects of complex educational interventions to deprescribe single or a relatively few medicines from therapeutic categories. In the Australian context, for example, Bolton *et al* (111) investigated a quality assurance activity involving GPs undertaking medication review to reduce inappropriate polypharmacy in their community living older patients. Sixty-two GPs from four geographic locations participated, each with up to 12 patients aged ≥65 years with polypharmacy. The intervention consisted of: two training workshops for GPs (one focussed on cardiovascular medicines and the other on psychotropic medicines); the GP conducting a medication review with the patient which involved taking a comprehensive medication history, identification and discussion of any medicine-related problems, and development of an action plan; and the GP conducting a follow-up medication review with the patient at six months. Of the 694 patients enrolled in the study, 640 had one or more medication reviews completed. At baseline, the median age of participants was 74 years (IQR 61-98) and median number of medications taken was nine (IQR 7-11). The authors found that for the 484 patients who had two medication reviews, the intervention was associated with a statistically significant reduction in the total number of medications ($p < 0.00005$ using the Wilcoxon sign-rank test). They also observed a reduction in the dose ($p = 0.028$) and frequency ($p = 0.0077$) of benzodiazepine prescriptions, and an increase in the number of selective serotonin reuptake inhibitors (SSRI) antidepressants used ($p = 0.0075$). These results suggest that medication review by GPs of patients with complex care needs can reduce the median number of medications that patients take. This study was limited by the lack of a control group, failure to describe how GPs were recruited to the study and consequently how they selected patients (such that selection bias was probable), and possible reporting bias by GPs who self-reported changes to medicines. Patient dropout was also an issue with only 484 (82.9%) of 584 patients completing both the first and second medication review. The clinical significance of this intervention remains unknown but it suggests that interactive training workshops targeting single therapeutic classes are effective in reducing medicine use. It remains unknown if an interactive workshop targeting multiple medicines would be effective in reducing the overall number of medicines and what the clinical consequences may be.

Pit *et al* also investigated the effectiveness of an educational QUM program, delivered at the level of general practice, to reduce a range of PIMs (but also promote the use of a

small number of other medicines such as thiazide diuretics as first line choice for hypertension) in Australia. (112) The primary outcome was a composite score reflecting use of just three of the medicines which had been targeted - non-steroidal anti-inflammatory drugs (NSAIDs), low dose thiazide diuretics and long-term benzodiazepine use - in community living Australians aged 65 years and over. Twenty GPs and 849 patients participated in the cluster Randomised Controlled Trial (RCT). The intervention comprised three main elements: education of the GP (i.e. academic detailing provided by a pharmacist skilled in medication review for nursing-home patients, provision of prescribing information and feedback), medication risk assessment completed by the patient, and GPs conducting a medication review and completing a checklist with their patients. In the control group, patients completed the medication risk assessment and GPs received no intervention except for participating in a clinical audit to encourage involvement in the study, which included feedback on medication risk factors and reviews conducted. The follow-up period was 12 months. Compared with the control group, at four months follow-up, participants in the intervention group had reduced odds of using NSAIDs (OR 0.62, 95% CI 0.39 to 0.99) and showed a non-significant reduction in use of benzodiazepines (OR 0.51, 95% CI 0.20 to 1.30) and thiazide diuretics (OR 0.70, 95% CI 0.48 to 1.01). Changes in medicines use were not significant at 12-month follow-up. At 12 months, intervention-group participants had lower AORs for having a fall (AOR 0.61, 95% CI 0.41 to 0.91), fall-related injury (AOR 0.56, 95% CI 0.32 to 0.96), and fall-related injury requiring medical attention (AOR 0.46, 95% CI 0.30–0.70). However, study authors conceded these results were not wholly explained by changes in medicines, and that broader effects of the intervention (e.g. assessment and management of postural hypotension) may have been at least partly responsible, or the effects may reflect a false positive (type 1) error. Quality-of-life scores using standardised instruments were unaffected by the intervention. While the study design was, in many respects robust, a key limitation was the recording of the usage of three target drugs as a crude measure of appropriateness for which recording or evaluation of the indications for prescribing were not performed. Still, the study results suggested this type of intervention was feasible, that it did not adversely affect quality of life, and that the process of medication review facilitated by the patient's usual GP may have conferred other benefits beyond those intended.

Two recently published cluster RCTs conducted overseas investigated the effect of a multifaceted educational intervention delivered to GPs. The studies used population level

prescribing data to identify a range of PIP criteria to be targeted for improvement by the GPs and measured effects accordingly. (113, 114) The first study, conducted in Norway, investigated the effect of educational outreach visits, and audit and feedback on PIMs in older people, using GPs as academic detailers within existing continuing medical education (CME) small groups.(113) Control participants received another educational intervention targeting antibiotic prescribing practice for respiratory tract infections. Potentially inappropriate prescriptions according to lists of explicit criteria were measured as the number of new PIPs (from a list of 13 different medications) for each of the one-year observation periods. A total of 449 GPs (96.6%) completed the study; 250 in the intervention group and 199 in the control group. After adjusting for baseline PIP differences and clustering effects at the peer CME group level, and employing a difference-in-differences analytic method, a reduction of 10.3% (95% CI 5.9 to 15.0) potential inappropriate prescriptions per 100 prescriptions per patient 70 years and older was obtained in the intervention compared to control group between baseline and study end.

A second cluster RCT, OPTI-SCRIPT, conducted in Ireland, investigated the effect of a complex, multifaceted intervention to reduce prescribing of the top five nationally reported PIMs (maximum dose proton pump inhibitors for >8 weeks, long-term NSAIDs and benzodiazepines, therapeutic duplication and tricyclic antidepressants with an opiate or calcium channel blocker). The intervention targeted GPs and incorporated one 30-minute academic detailing session with a pharmacist, review of medicines by GPs supported by web-based pharmaceutical treatment algorithms, and tailored patient information leaflets. Control practices received basic, patient-level prescribing feedback. Two primary outcomes were used: 1) the proportion of patients with PIMs, a composite measure capturing any number of the predefined PIMs in the study to address multiple PIMs in individual patients; and 2) the mean number of PIMs per group. Twenty-one practices and 190 patients were followed. Outcome data were collected approximately four to six months after baseline data collection. Compared to control, patients in the intervention group had significantly lower odds of having PIMs (AOR 0.32, 95% CI 0.15 to 0.70, p = 0.02). The mean number of PIMs per group in the intervention group was 0.70, compared with 1.18 in the control group (p = 0.02) but this effect was principally achieved through reduced prescribing of proton pump inhibitors at maximal dose (AOR 0.30, 95% CI 0.14-0.68, p = 0.04).

These two studies show that complex educational interventions delivered to GPs, targeting explicit lists of PIMs, and informed by national population prescribing data, reduce prescribing of PIMs in the short-term but the clinical relevance and impact on long-term outcomes remain unknown. The use of explicit lists may provide an entry point to deprescribe one or more PIMs, but achieving reductions in a larger number of medications requires identification of all medicines which are actually or potentially inappropriate at a patient level by means of a more nuanced, individualised decision-making process.

One recent study of an intervention to support review and minimisation of potentially inappropriate polypharmacy based on implicit criteria was the mixed methods pilot study published by Muth *et al*. (115) The complex intervention targeted GPs in prioritising medications in community dwelling people ≥65 years of age with ≥3 chronic conditions and ≥5 chronic prescriptions across 20 general practices in Germany over 12 weeks. The intervention comprised medication reconciliation and training in using, during patient consultations, a computerised decision support package that provided prompts for identifying and minimising potentially inappropriate polypharmacy (but also undertreatment of conditions such as pain). The primary outcome was a change in the MAI at the patient level, which was not shown to be statistically significant at study end. One of the key reasons for the lack of an apparent change in MAI was that the baseline scores were very low (indicating a high pre-existing level of medication appropriateness), leaving very little scope for a further decrease in MAI scoring. (115) Other exploratory outcomes included quality of life, functional status and adherence-related measures for which no statistically significant differences between groups were seen. Although the intervention was shown to be feasible and without harm in the short-term, it did not lead to any overall improvement in medication appropriateness or improvement in function or quality or life, although the short timeframe was a limiting factor.

In summary, while use of explicit appropriateness criteria may improve QUM, interventions that support GPs in taking an individualised approach to deprescribing in older people with polypharmacy using more wholistic decision guides or frameworks may realise greater effects. This is discussed in more detail below.

2.3.4 Structured guides to assist deprescribing

As a secondary publication to this thesis, a narrative review of structured guides for deprescribing was recently published. (86) The full publication is available at http://ejhp.bmj.com/content/24/1/51). Structured guides are those that take the clinician

through sequential steps in deciding which medications used by an individual should be targeted for discontinuation after due consideration of relevant contextual factors. They take account of the interactive complexity of polypharmacy and prompt a more systematic appraisal of all medications being used. (86) As low self-efficacy in deprescribing has been identified as a key barrier for GPs, (9) structured guides depicting a logical sequence of decision steps which are easy to assimilate and apply to patient care may support GP-led deprescribing. (86)

Two guides focus on deprescribing in older patients – 'The Good Palliative-Geriatric Practice' (GPGP) guide and 'Confirm, Estimate, Assess, Sort, Eliminate' or 'CEASE' guide - and both have been subject to a process of development and refinement over time involving prescribers from different subspecialties and pharmacists. (86) The GPGP starts by querying if an evidence base exists suggesting benefit of a medicine in its current dose, given a patient's age and level of disability, and whether such benefits outweigh all known adverse effects. If the answer is no, then the drug should be discontinued. Furthermore, if adverse effects are apparent from a medicine that otherwise is indicated because of strong potential for benefit in disease-related outcomes, then it should be changed to an alternate medicine or continued at a reduced dose. (103) The GPGP was first designed for application to disabled patients in the nursing home setting (103) and later applied to a group of non-palliative community dwelling adults. (102)

The CEASE framework is a five-step guide and a condensed form of an earlier ten-step protocol developed by the same research team (20, 116). It provides a more granular decision framework for clinicians than the GPGP and is outlined in Appendix 2. CEASE was originally designed for application in the hospital setting, but has assumed different forms according to the needs of different health settings. (91) Neither the GPGP or CEASE guides have had their evidence of effectiveness tested in randomised controlled trials. (91) Studies evaluating the use and effects of the GPGP and CEASE are considered below.

2.3.4.1 Good Palliative-Geriatric Practice (GPGP) Guide

The GPGP was first applied to 119 disabled patients in six geriatric nursing departments and compared with 71 control patients within the same wards and who were cared for by the same treating physicians. Intervention and control patients were of comparable age, gender and comorbidities and it is noteworthy that 94% and 93%, of the intervention and control group, respectively, had moderate to severe dementia. (103) After 12 months follow-up, 332 different medications were discontinued among intervention patients (mean

2.8 medicines per patient), compared with no change among controls. Medicine discontinuation was not associated with significant adverse effects. The overall rate of medicine discontinuation failure (i.e. onset of withdrawal syndromes prompting re-initiation or up-titration in dose) was 18% of all patients and 10% of all medicines. The 12-month unadjusted mortality rate was 45% in the control group versus 21% in the intervention group ($p<0.001$), while the annual referral rate to acute care facilities was 30% compared to 12% ($p<0.002$). Key limitations of this study include failure by the study authors to disclose the process of patient recruitment and sampling (leaving this author to assume that a convenience sample was used, introducing the potential for significant selection bias) and the absence of intra- or inter-rater reliability in the guide's application. The generalisability of these study findings to older patients without dementia is also questionable.

The algorithm was next evaluated in a prospective cohort feasibility study in a consecutive sample of non-palliative, community based older adults. (102) Participants were referred to a hospital geriatric clinic by their family physician or family members for comprehensive geriatric assessments. Geriatricians applied the GPGP to 70 eligible multimorbid community based adults. Discussions were held with patients and carers and then the geriatrician wrote letters to each individual's family physician requesting them to stop as many 'non-life saving drugs' as possible for at least 3 months. Patients were of mean (SD) age 82.8 years (6.9) and used a mean (SD) of 7.7 (3.7) medications. The application of the algorithm by the geriatrician recommended discontinuation of 4.4 (2.5) medications per patient, corresponding to discontinuation of 311 medications in 64 patients. Mean follow-up was 19 months and successful discontinuation was achieved in 81% of cases. No significant adverse effects or deaths were attributable to discontinuation and 88% of patients reported global improvements in health, although the authors did not divulge how this was evaluated. Important limitations of this study included: failure to detail participant recruitment and sampling, introducing the risk of selection bias, although the study authors stated a consecutive sample of patients was used; the lack of a control group; and failure to evaluate intra- and inter-rater reliability. An interesting feature of the study design however, was that researchers optimised the chance of GPs and the patient/family members accepting the geriatrician's recommendations to deprescribe medicines because the request was solicited in response to the GP or patient's family identifying a deterioration in the patient's clinical trajectory. (102)

2.3.4.2 CEASE Guide

The first study examining the utility of CEASE aimed to determine the effects of the guide on clinician prescribing intentions. (117) Sixty-one clinicians (19 consultant physicians, 17 medical registrars, seven interns/residents and 17 clinical pharmacists) were presented with clinical information about a hypothetical 81-year-old female patient with 12 chronic diseases, receiving 19 different medications. On a standardised, anonymous form, each participant indicated, as a pre-test, which medications they felt strongly inclined to discontinue or continue. The guide was then presented and participants were asked to review the case again, repeating the medicine selection process. Among the entire cohort, the mean (standard deviation [SD]) number of medications selected for discontinuation increased from 6.0 (2.7) pre-test to 9.6 (3.2) post-test ($p<0.001$). The greatest increases seen were among consultant physicians (6.6 [2.3] to 11.5 [2.9], $p<0.001$) and clinical pharmacists (5.3 [2.6] to 8.9 [2.2], $p<0.001$). (117) Although limited by the application of the guide to a hypothetical case by a convenience sample of hospital clinicians at a single point in time, this study suggests CEASE could facilitate deprescribing of PIMs by reducing clinician uncertainty.

The efficacy of CEASE has also been evaluated in a prospective cohort study of 50 hospitalised patients. Patients were of median age 83 years, had six comorbidities and were in receipt of eight or more regular medications. Participating clinicians comprised six consultants, six medical registrars, eleven interns and three clinical pharmacists. Application of the guide led to the discontinuation of 186 of 542 regular medications (34.3%), representing a clinically significant reduction in the median (interquartile range [IQR]) number of medications per patient at discharge (7 [5–9]) compared to that at presentation (10 [9–12] $p<0.001$). (118) The classes of medicines most frequently ceased were statins, gastric acid suppressive agents, ACE inhibitors/angiotensin receptor antagonists and inhaled bronchodilators. Thirty-nine of the 50 patients had follow-up status ascertained at a median of 78 days, and only 5 of 413 (1.2%) ceased medications were recommenced among three patients due to symptom relapse. There were no instances of hospital readmissions or ADEs arising from deprescribing. This pilot study was limited by the use of a small convenience sample of patients from one tertiary centre (limiting the generalisability of results to more robust older patients in different care settings), the lack of a control group, and failure to determine intra- and inter-rater reliability. However, results do indicate that CEASE provided a feasible and effective

method of medication review for application by a range of clinicians in the hospital setting. Further testing is required to evaluate its feasibility of use by clinicians and impact in other care settings.

Overall, the evidence pertaining to the application of deprescribing frameworks in older people is very limited. More research is needed determining the effectiveness and ease of use of these guides, as part of a broader intervention, in routine clinical practice, especially in primary care. These guides are worthy of further investigation as they may provide a mechanism by which clinicians can negotiate the uncertainty of undertaking proactive review of all medications in older patients with a view to identifying and minimising potentially inappropriate polypharmacy.

2.3.5 Challenges of deprescribing

The current behaviour of clinicians to overprescribe or continue PIMs in some older people with polypharmacy is better understood when both the drivers for PIMs (as previously detailed in section 2.2.2, 'Drivers of polypharmacy') and the difficulties associated with deprescribing are considered. Regarding the latter, the act of stopping a medication prescribed over preceding months to years is complicated by many factors at both the patient and clinician level, and which need to be examined if effective deprescribing strategies are to be developed. These factors operating within the patient-clinician dyad are compounded by organisational and health system factors that add further challenges to deprescribing. For example, GPs, in reviewing medications of their patients with multiple conditions, have to deal with the recommendations of multiple specialists across different care settings. For this reason, it has been proposed that an interdisciplinary effort, focussed on the wholistic health needs of the patient, is required when managing older patients with multimorbidity and polypharmacy. (119)

Patient goals and expectations regarding deprescribing is an unstudied area of research. A review by Reeve *et al* however, identified several patient barriers to, and enablers of, deprescribing. (8) A belief that the medication is appropriate, fear of, or difficulties in, stopping medications, and previous negative experience with medicine discontinuation were some of the main barriers to deprescribing. Conversely, actual or feared adverse effects of continuing medications, benefits of stopping, a dislike of medications, reassurance that a medication could be restarted if needed, and the support and influence of their primary care clinicians were identified as facilitative factors for patients in deprescribing.

A similar review of prescribers' barriers and enablers to deprescribing was undertaken as part of this PhD project (see Chapter 4). The key findings of this review demonstrated that the reasons prescribers continue or do not stop PIMs are multifactorial and highly interdependent. Barriers and enablers to minimising PIMs emerged within four analytic themes: awareness of examples of PIMs and the problem of potentially inappropriate polypharmacy; clinical inertia secondary to PIM cessation being viewed as a lower value proposition compared with their continuation; self-efficacy regarding ability to alter prescribing; and feasibility of altering prescribing in routine care environments given external constraints. (9) There is a dearth of qualitative literature assessing the views of other clinicians, such as nurses and clinical pharmacists, towards deprescribing in older people in the primary care setting.

Comparison of these two reviews suggests that prescribers' barriers are concordant with those of patients with respect to resistance to change, poor acceptance of non-drug alternatives, and fear of negative consequences of discontinuation. However, GPs in particular appear to underestimate their capacity to influence patients to stop medications. In the presence of a PIM, GPs could explore and leverage enabling factors from the patient's perspective, such as negative experience/s with, fears and dislike of, medications and the assurance that a ceased/reduced dose medication could be recommenced or increased if necessary. (8)

It is well established that knowledge of pharmacology is not the only factor impacting prescribing decisions. (120) Rather, these decisions result from interacting clinical, social and cultural factors impacting on both patient and prescriber. (120-122) Facilitating effective and sustainable behaviour change must target the determinants of a prescribing behaviour. (123) The National Institute of Clinical Excellence (NICE) advocates for the identification of clinician barriers to change as a critical step in developing interventions to effect change in primary care. (40) This is not to suggest that patient barriers to change are any less important, but simply that clinicians, and certainly GPs, offer an entry point for patients to be brought into a discussion on the pros and cons of deprescribing.

2.4 Changing practice in primary care

Nearly all changes in primary care involve complex interventions, i.e. those with multiple components that interact. (124) Components may occur at one or more levels, for example: at an individual professional level, e.g. to influence a clinician's diagnostic or treatment decisions; at an organisational level, e.g. (re)allocation of duties to other

members of the multi-disciplinary team; or at a system level, through altered funding arrangements or changes to policy or legislation. (125) To date, the overwhelming majority of interventions have examined strategies to effect change at the individual professional level. (126)

Chauhan *et al* published a systematic review of reviews in 2017 evaluating the evidence on behaviour change interventions and policies directed at primary care clinicians. (127) One hundred and thirty-eight reviews (including systematic reviews, overviews of reviews, scoping and rapid reviews, and health technology reports) representing 3502 individual studies in developed countries were included. (127) The authors summarised findings based on the authors' conclusions, qualitative data, quantitative data with statistically significant group differences in terms of patients' and providers' outcomes, and methodological quality. All behaviour change interventions and policies identified from the data were classified according to the behaviour change wheel framework proposed by Michie *et al*. (128) This framework describes the interplay between behaviour, intervention and policy and describes nine intervention types: education (to increase knowledge or skills), persuasion, incentivisation, coercion, training (imparting skills), restriction, environmental restructuring (e.g. changing the physical or social context), modelling (providing an example for people to emulate) and enablement (increasing means/reducing barriers to increase capability or opportunity to change, beyond education and training and environmental restructuring). (128)

Most systematic reviews (91%) investigated behaviour and practice changes among family physicians (i.e. GPs) managing patients with chronic disease. Twenty-eight reviews evaluated educational interventions, which included continuing medical education programs, academic detailing (visits by trained health professionals in the doctor's place of work) and small group learning workshops. Some educational interventions were evaluated as components of multifaceted education interventions, and thus combined with reminder systems and audit and feedback, whereas others were not. Sixteen reviews evaluated the use of information technology (IT) including interactive analysis systems, clinical decision support systems and the use of electronic health records and prescriptions. Considering evidence from moderate to high quality reviews, interactive and multifaceted education programs, training with audit and feedback, and computerised clinical decision support systems were shown to be beneficial in improving clinician

knowledge, optimising prescriptions, enhancing patient outcomes, and reducing adverse events. (127)

Although the evidence was limited, changing the physical or social context (including the use of collaborative or shared-care practices or the institution of specialist nurses or pharmacists to primary care practices) and the use of behaviour modelling (i.e. local opinion leaders providing an example for others to emulate) appeared promising in improving professional collaboration and adherence to guidelines, respectively. Interventions shown to be ineffective included financial incentives to family physicians (to facilitate long-term behaviour change) and passive guideline dissemination. (127)

This was a large and comprehensive overview of reviews, meaning that the findings are highly generalisable to physicians in primary care in developed countries. A clear limitation was the inability to quantify the magnitude of effects due to the heterogeneity of included reviews, primary care contexts, and diversity of the outcomes being examined in each review. Another limitation, perhaps because it was a review of reviews, was failure to indicate the time over which the interventions were implemented, the duration of any beneficial effects, time to decay and the frequency or need for follow-up interventions to ensure the sustainability of effects. Despite these limitations, this reviews' findings were consistent with earlier systematic reviews which have found that active and multifaceted educational interventions targeting different barriers to change are more likely to be effective than single, passive interventions in changing prescriber behaviour. (129, 130) Specifically, the literature suggests the following elements should be considered in designing an effective and workable complex intervention to change primary care physician behaviour:

- Systems change, for example, using computerised decision support and electronic health records to support change in practice;
- Education and training around the focus of change;
- Role modelling using key opinion leaders and/or senior clinicians to champion the trialling and adoption of new and better ways of doing things; and
- Audit and feedback, that is, having a process for monitoring and reflexive learning through the provision of data pertaining to the physicians' performance

2.4.1 The potential facilitative role of consultant pharmacists in Australia

The findings of the review by Chauhan *et al* (127) that collaborative models of care, involving the placement of specialist pharmacists within primary care practices to facilitate practice change, warrants further investigation. In Australia, pharmacists are key health professionals in promoting QUM. This raises the question, that, depending upon factors that GPs identified as barriers to deprescribing, what role, if any, could pharmacists play in supporting a multifaceted, GP-led deprescribing intervention in primary care? Speculation on this issue in the Australian health care context was based on two factors: (1) the current policy context promoting greater collaboration between pharmacists and GPs in primary care; and (2) evidence that pharmacist-led interventions may improve prescribing appropriateness in community living older adults.

The call for greater collaboration between pharmacists and GPs in primary care in Australia has stemmed from the demonstrated enhanced role and impact of pharmacists, particularly when integrated into the general practice team. (37) For example, integrating a pharmacist into general practice has been associated with an increase in the timeliness and completion rate of medication reviews and greater acceptance and implementation of pharmacist recommendations by GPs. (131, 132) A systematic review also found that pharmacists co-located in general practice clinics led to improvements in chronic disease management and quality use of medicines, primarily through medication review services. (38) Furthermore, a recently published systematic review found that medication reviews undertaken by pharmacists in physician practices, where there was access to comprehensive medical notes and feedback to physicians, may improve prescribing appropriateness in community living older adults. (133)

In Australia, medication review services are funded through the Sixth Pharmacy Guild Government agreement. (36) Pharmacists accredited to undertake comprehensive medication review are referred to as consultant pharmacists (CPs). Most consultant pharmacists work external to GPs' practices, but an increasing number are being integrated within general practice teams. (134) It was therefore proposed that involvement of a consultant pharmacist could be one worthy element of any multifaceted GP-led deprescribing intervention.

2.5 Summary

Given the significant burden associated with potentially inappropriate polypharmacy in many community living older people, including ADEs, decreased physical and cognitive functioning, and increased risk of falls, geriatric syndromes, hospital admissions and death, there is an urgent and growing need to minimise this harm. The evidence of efficacy of deprescribing interventions to date, however, is limited.

Deprescribing of single medications/therapeutic categories appears feasible and safe in the short-term. Single studies have shown modest short-term effectiveness for selected outcomes which vary depending upon the therapeutic category being targeted. Meta-analysis of deprescribing interventions to minimise potentially inappropriate polypharmacy across multiple health settings have shown little to no impact on clinically meaningful outcomes to date. Deprescribing interventions appear to have no effect on mortality, although a beneficial effect is apparent if interventions are patient-specific and decisions are fully informed by the clinical context. Studies evaluating deprescribing interventions to reduce potentially inappropriate polypharmacy do not indicate that deprescribing reduces hospitalisations, medication burden, ADEs, or occurrence of first falls or lead to improvements in quality of life. However, in participants who did fall, deprescribing appears to reduce the number of subsequent falls. These findings are limited by high study heterogeneity, low-numbers of events, low-quality and relatively short follow-up for the outcomes being measured. Furthermore, almost without exception, the studies included in these reviews were led by an investigator or clinician, who, unlike a GP, did not have an ongoing therapeutic relationship with, and tacit knowledge of, the patient. Leveraging an existing therapeutic relationship may lead to greater patient involvement in the decision-making process which, in turn, may guide and support deprescribing.

Single studies that have examined the impact of GP-led interventions in community living older people with up to 12 months follow-up, have demonstrated improvements in prescribing quality and medication burden. These studies have involved multifaceted educational interventions for GPs, a central component of which has been the provision of an explicit list of PIMs which should be avoided. Whilst feasible and effective, the longer-term impact of these interventions on clinically meaningful outcomes remains unknown. A key difficulty of the use of such explicit lists is that, in the Australian context, medicines commonly identified as being potentially inappropriate, account for relatively few ADEs. Therefore, feasible strategies are required which support the identification of medicines

which are inappropriate at an individual patient level after considering the clinical context. Deprescribing decision guides or frameworks could form part of such a strategy but more research is needed in determining the effectiveness and ease of use of these guides in routine clinical practice, especially in the primary care setting.

Changing practice in the primary care setting is challenging. Multifaceted educational interventions targeting GPs, and which account for the context in which change is to occur, have been shown to be effective. Furthermore, quality improvement interventions in which front-line clinical staff have been engaged to identify local barriers and enablers to change and then use this knowledge to inform intervention design, have been shown to be more likely to be implemented and therefore effective.

General practitioners, with long-term therapeutic relationships with patients, offer an entry point to facilitate deprescribing with patients. Given the policy context to see greater GP and pharmacist collaboration in primary care in Australia, it was speculated that CPs could be supportive to GPs in this process, and help overcome factors that GPs identified as potential barriers to deprescribing in routine care.

The overarching aim of this study therefore was to develop and pilot a multifaceted GP-led intervention to minimise potentially inappropriate polypharmacy in community living older people, addressing GP and CP barriers and enablers to deprescribing in routine care. The three specific aims of the study were to:

- Investigate prescribers' perspectives on factors which shape their behaviour towards continuing or discontinuing PIMs in adults (Phase 1);
- Explore the views of a sample of GPs and CPs about potentially inappropriate polypharmacy and the reasoning they apply to deprescribing in older people in primary care, including factors that influence this process (Phase 2); and
- To evaluate the feasibility, effectiveness and safety of a multifaceted GP-led intervention in community living older people in primary care, developed from Phases 1 and 2 (Phase 3).

Chapter 3 Research Approach

In Chapter 2, the need for research into a GP-led deprescribing intervention to minimise potentially inappropriate polypharmacy in community living older Australians was established. The principles of behaviour change to be considered in the design of a complex intervention in primary care were also outlined. In this chapter, the research approach, informed by the United Kingdom (UK) Medical Research Council (MRC) guide to complex interventions is described. The research paradigm utilised in this investigation and an overview of the three-phased, mixed methods research design is then presented. Detailed methods corresponding to each of the three phases will be described in later chapters. The methods for Phases 1 and 2, which are qualitative in nature, are presented in Chapters 4 and 5, alongside findings for each of those phases. Detailed methods for the Phase 3 exploratory study are presented in Chapter 6, as a standalone methods chapter.

3.1 Research approach

Changing the behaviour of health professionals to improve patient care is often difficult, especially in primary care, due to the complex relationships between health professionals and patients, and the organisational, social, cultural and geographical systems in which both parties operate. (40, 135, 136) Consequently, nearly all changes in healthcare, including primary care, involve complex interventions, i.e. those with multiple components that interact. (124) Supporting GPs to facilitate deprescribing with their community living older patients is no exception. Factors influencing the prescription and use of PIMs and barriers to deprescribing are broad and multi-dimensional. (8, 9) As outlined in Chapter 2, evidence to date suggests that multifaceted educational interventions, which address locally identified barriers to change, in a given care context, increase the likelihood of implementation and effectiveness. (40, 127) Moreover, evidence to date suggests the design of complex interventions in primary care should consider principles of behaviour change such as systems change (e.g. using information technology and computerised decision support), education and training, role modelling and audit and feedback. (127)

The UK MRC offers guidance on, rather than a prescriptive approach to, the design and evaluation of trials of complex health interventions. (124). Complex interventions are defined as those comprising a number of separate elements which seem essential for the intervention's effectiveness, although the 'active ingredient' and contribution of each ingredient, both relative and collective to the outcome, can be difficult to determine. (124)

The MRC guidance describes key elements associated with the design and evaluation of complex interventions, three of which were considered within scope of this thesis, as outlined in Figure 3-1, which has been adapted from Craig *et al,* 2013. (137) The MRC has also advocated the use of qualitative research methods in addition to quantitative methods, to better understand how and why something happens, either in the initial development or evaluation of an intervention, or both. (138, 139)

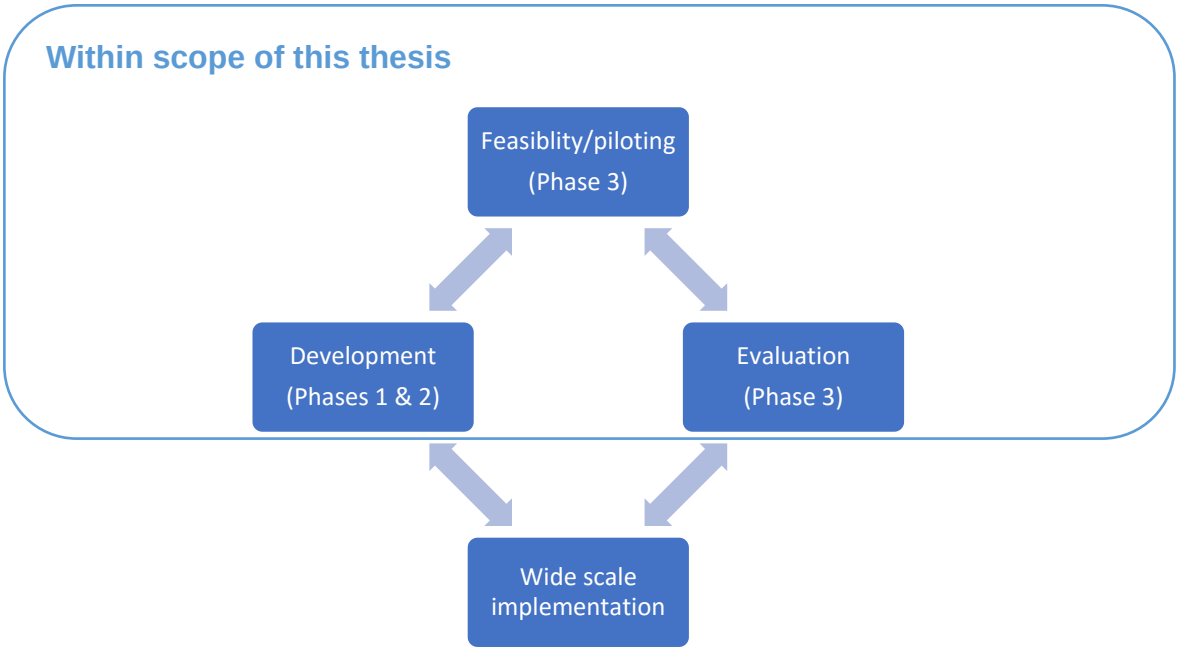


FIGURE 3-1 KEY ELEMENTS OF THE DEVELOPMENT AND EVALUATION OF A COMPLEX INTERVENTION

In the development phase, the MRC guidance is that a sound theoretical understanding of the research problem and how an intervention may cause change is crucial, so that any knowledge and/or practice gap can be addressed in the design of an intervention. (137) The framework also highlights the importance of feasibility or pilot testing an intervention and conducting a thorough evaluation including both process and outcome measures before widescale roll-out and implementation. The rationale for this is that the evaluation of complex interventions is often undermined by issues pertaining to implementation (i.e. recruitment, intervention delivery, acceptability, compliance). Therefore, undertaking a process evaluation may assist in determining if any lack of effect is due to genuine ineffectiveness of the intervention, rather than implementation challenges or failure. (137)

Informed by the MRC guidance, a three-phased, mixed methods design was used to address the overarching study aim to develop and pilot a multifaceted GP-led intervention

to minimise potentially inappropriate polypharmacy in community living older people, addressing GPs' and CPs' barriers and enablers to deprescribing in routine care. The three phases, specific aims and how they mapped to the UK MRC guidance,(137) are detailed in Figure 3-2 below. In conceptualising the scope of this study, this work is developmental, and will help inform a future, longer-term, large-scale cluster RCT for further evaluation and potential widescale roll-out into primary care.

FIGURE 3-2 THREE PHASES OF THE RESEARCH STUDY ALIGNED WITH KEY PHASES FROM THE UK MRC FRAMEWORK

Ch = Chapter.

In conducting mixed methods research, Creswell and Plano Clark describe four foundational worldviews which can be used: post-positivism; constructivism; transformation; and pragmatism. (140) Given the ultimate intention for these research findings to be applied (i.e. to facilitate deprescribing by frontline clinicians to minimise potentially inappropriate polypharmacy in older people), a pragmatic paradigm was utilised for this project. Pragmatism is a common paradigm used in applied health services research for the very reason that it is oriented towards real world practice. (41, 42) Pragmatism also offers a 'paradigm of choices' (141), prioritising the usefulness and

efficiency of methodological approaches over philosophical purism which may otherwise constrain methodological choice. (42)

3.2 Research design

An exploratory mixed methods design was used to address the specific research aims. (140) The first two sequential developmental qualitative phases were used to provide a greater understanding of the context for change and aid in the development of key elements of the multifaceted deprescribing intervention to be piloted in the exploratory study in the third phase. In this third phase, qualitative data relating to the feasibility and experience of all parties participating in the intervention was used to elaborate and explain key quantitative results on its effectiveness. (140)

Phase 1 was the systematic review and thematic synthesis of qualitative studies that explored prescribers' perceived barriers and enablers to minimising potentially inappropriate medications (PIMs) that are chronically prescribed in adults. This developmental phase was required to maximise the likelihood that the design of the intervention would be concordant with, and able to address, real-world needs and concerns of practising clinicians in undertaking deprescribing. A broad systematic review of the literature, not restricted to type of prescriber or age of adult patient, was conducted. It was specified *a priori*, that, depending upon the studies yielded, sub-analyses by prescriber type, care setting and/or patient age could be subsequently undertaken to ensure the generalisability of findings to GPs caring for community living older people in primary care.

Phase 2 was developmental and explored the views of a sample of GPs and CPs about potentially inappropriate polypharmacy and the reasoning they apply to deprescribing in older people in primary care, including factors that influence this reasoning process. A qualitative descriptive design was employed incorporating the focus group method. (142) Qualitative description is an appropriate choice in health services research based on mixed methods where a key purpose is to ascertain professional's views on a particular topic. (142) The Framework method was used to discern major and minor themes from the data. (143) The purpose of conducting the focus group discussions in the context of the overall study design was two-fold: 1) to further develop a theoretical understanding of the anticipated process of change (or barriers to it) in the local context; and 2) inform the elements of the deprescribing intervention most likely to support local GPs and CPs in undertaking deprescribing with their patients.

Phase 3 was the exploratory mixed methods study, to assess the feasibility, effectiveness and safety of the intervention to facilitate GP-led deprescribing in community living older people in primary care. A non-randomised, controlled pre-post mixed methods design was used. Both quantitative and qualitative data were collected and analysed to assess the feasibility and impact of the intervention. The study involved a convenience sample of five general practices and twenty GPs in Metropolitan South-East Queensland across two study arms. The intervention was targeted at the level of the clinician, with quantitative and qualitative measures gathered at the clinician and patient level. Quantitative data were collected from the usual care and intervention group before and after exposure to the intervention regarding the intervention's effectiveness. Qualitative data were collected at follow-up by semi-structured interviews involving GPs and patients who participated in the intervention. Data were collected to explain quantitative findings, (140) and examine aspects of the feasibility and implementation of the intervention, including adoption of each of its elements, acceptability, and the likelihood of sustainability in routine care. (144) An overview of the study design and timing of data collection is shown in Figure 3-3, but detailed information pertaining to study methods is presented in full Chapter 6.

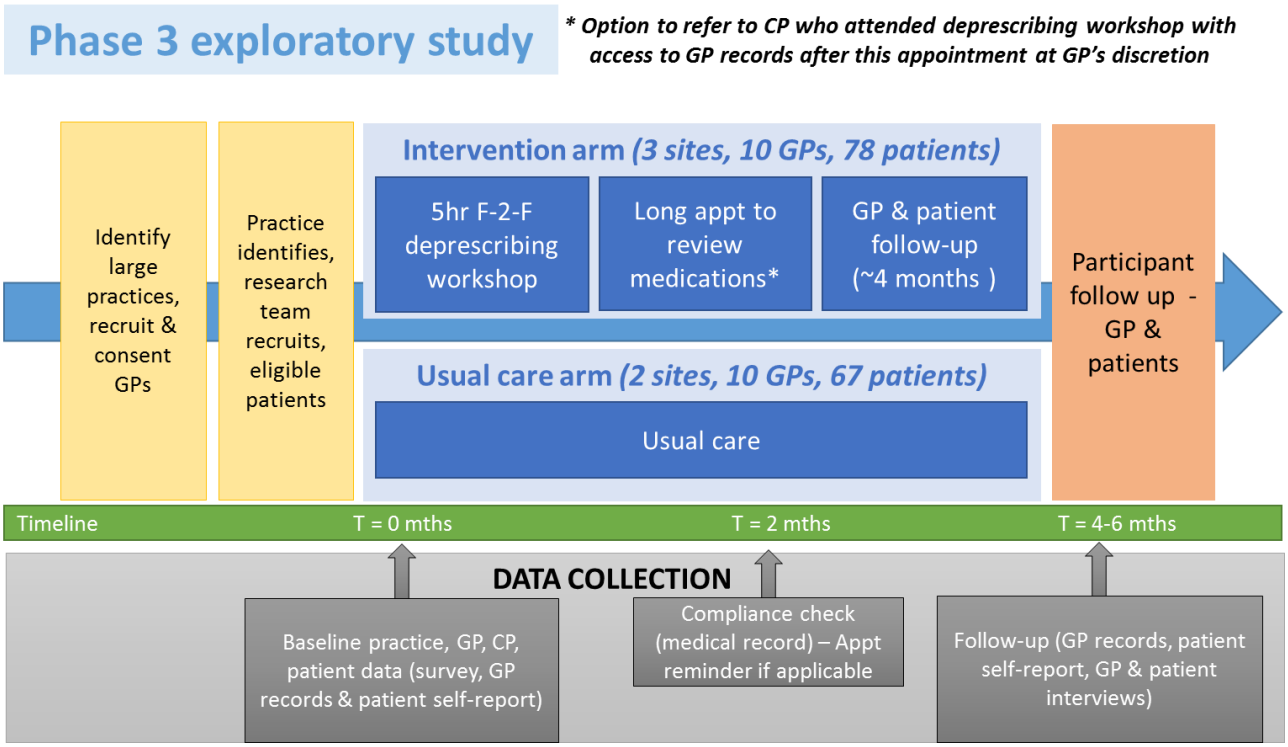


FIGURE 3-3 PHASE 3 EXPLORATORY STUDY DESIGN OVERVIEW

(F-2-F = face-to-face; appt = appointment).

3.3 Methodological and ethical considerations

The key ethical issues for this study pertained to recruitment, informed consent, privacy and confidentiality. With regards to recruitment of general practice sites, GPs, CPs and patients, at no point was an individual's or organisation's details provided to the research team without prior permission from the party, unless that information was publicly available without restriction. The recruitment of patients to the study by the research team, rather than their GP, minimised the potential for power asymmetries in the doctor-patient relationship to affect patients' decisions to participate.

Informed consent was acquired from all participants by the research team members before partaking in the study. At all stages of the study, it was made clear that participation was entirely voluntary and that withdrawal from the study would bear no negative consequences for the individual in any way.

All personal details of participants and information provided to the researcher were kept confidential and stored on a secured server. Data were stored in a de-identified manner with a master list of each participant's name and unique identifier kept in a password protected document separate to the participant's data coded by unique identifier. All information was reported in de-identified format.

For Phase 2 focus group discussions, there were no foreseeable added risks above the risks of everyday living as clinicians provided personal perspectives and opinions and chose the amount and extent of information revealed. For the exploratory study in Phase 3, there were two additional ethical considerations. Firstly, although the potential for patient harm was assessed as minimal because at all times, the patient's usual GP would remain responsible for patient care, a protocol to alert the research team of any adverse events (actual or potential) arising from intervention was implemented. The adverse event form for completion and forwarding to the research team can be found in Appendix 3.

Secondly, through a small grant from Greater Metro South Primary Health Network, practices were able to access $1000 for generating a list of eligible patients who consented to be contacted by the research team. This figure was offered to recognise the time and resources that GPs, practice managers and administrative staff would spend in generating this list. The GPs and CPs were also eligible to receive $500 each in recognition of potential lost earnings as a result of attending the five-hour deprescribing training workshop. No additional remuneration was offered to clinicians for patient contact

time, i.e. any remuneration occurred through existing Medicare items for GPs and Community Pharmacy Agreement arrangements for CPs, should they be required to conduct a Home Medicines Review.

Ethical approval from the University of Queensland's Ethical Review Committee was obtained for Phase 2 and Phase 3 of the study, with Approval numbers 2014001296 and 2015000044, respectively. These approvals can be seen in Appendix 1.

Chapter 4 Phase 1 Systematic review and thematic synthesis

This chapter details the methods, findings and discussion of the Phase 1 systematic review and thematic synthesis, the aim of which was to synthesise qualitative studies that explored prescribers' perceived barriers and enablers to minimising potentially inappropriate medications (PIMs) chronically prescribed in adults. As advocated by the National Institute of Clinical Excellence, identifying clinician's barriers and levers to change are critical to the development of effective interventions to facilitate behaviour change, (40) and so this work was undertaken as a key developmental step under the UK MRC guidance. (124)

A broad systematic review of the literature, not restricting to type of prescriber or age of adult patient, was conducted for this first phase. It was specified *a priori*, that, depending upon the studies yielded, sub-analyses by prescriber type, care setting and/or patient age could be subsequently undertaken to ensure the generalisability of findings to GPs caring for community living older people in primary care.

The contents of this chapter have already been published as a standalone article in BMJ Open in December 2014, a full version of which is available online at http://bmjopen.bmj.com/content/4/12/e006544 . (9) Since publication in 2014, another 11 eligible studies have been published. The characteristics and key findings of these studies have been reported and synthesised in the context of the review's findings at the end of this chapter, in section 4.4 'Relevant studies published since 2014'.

4.1 Method

In the absence of a universally accepted method to conduct a systematic review of qualitative data, the principles of quantitative systematic review were applied to qualitative research, (145) with guidance from the Cochrane endorsed ENTREQ **(**Enhancing transparency in reporting the synthesis of qualitative research) position statement. (146)

4.1.1 Search strategy and sources

An initial search was conducted to ensure no systematic review on the same topic already existed. Two experienced health librarians were independently consulted in developing a comprehensive search strategy, which was informed by extensive prior scoping. (147)

PubMed, Embase, Scopus (limited to Health Sciences), PsycINFO, CINAHL and INFORMIT (Health Collection) electronic databases were searched from inception to

March 2014. Filters to identify qualitative research were used and adapted to improve search sensitivity. (148) These were combined with terms and text words for: medical and non-medical prescribers and either inappropriate prescribing or reducing, stopping or optimising medications. Terms/text words were searched in all/any fields or restricted to title, abstract or keyword, depending upon the size of the database and sophistication of its indexing. Reference lists and related citations of relevant articles were reviewed for additional studies. The full search strategy is detailed in Appendix 4.

4.1.2 Study selection

After duplicate citations were excluded, titles and abstracts were screened and where necessary full text read, to create a list of potentially relevant full text articles. Articles were required to meet provisional, intentionally overly inclusive, eligibility criteria to minimise the risk of inappropriate exclusions by the single reviewer. This list was forwarded to three members of the advisory team who independently assessed the articles for inclusion. Discrepant views were resolved by group discussion to create the final list of included papers based on refined eligibility criteria.

4.1.3 Inclusion and exclusion criteria

Inclusion criteria comprised: 1) original research articles with a qualitative component (i.e. qualitative, mixed or multi method studies all accepted); and 2) focus on eliciting prescribers' perspectives of factors that influence their decision to continue or cease chronically prescribed PIMs (as defined by the authors of each study) in adults. No limits were placed on the care or practice setting of the patient or prescriber respectively, or whether the article related to single or multiple medications.

Exclusion criteria comprised: 1) reviews, papers not published in English, and those for which the abstract or full text were not available; 2) focus on medication management decisions in the final weeks of life; 3) focus entirely on initiation of PIMs; and 4) reporting of only quantitative data derived from structured questionnaires.

4.1.4 Assessment of the quality of studies

Reporting of studies was assessed using the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist. (149)This reporting guideline, endorsed by the Cochrane Collaboration, assesses the completeness of reporting and potential for bias in studies of interviews or focus groups according to three domains: 1) the characteristics of the research team, relationship with participants and reflexivity; 2) the study design and

setting; and 3) transparency in data analysis and consistency and clarify in reporting of findings. (149) Any instances of interpretive uncertainty arising from the checklist were discussed and resolved with the broader advisory team.

Studies were not excluded or findings weighted on the basis of the COREQ assessment. Rather, the decision was made to include all studies, ascribing to the theory that the value of insights contained within individual studies may only become apparent at the point of synthesis rather than during the appraisal process. (150)

4.1.5 Data extraction process

For all included articles, data were extracted about study aims, location, setting, study design, participants, recruitment, PIMs examined, and prescribers' perspectives of factors influencing the chronic prescription of PIMs. Data for thematic analysis were only extracted from the results (not discussion) section of papers, with particular notice taken of quotations from prescriber participants.

4.1.6 Synthesis of results

The method used to synthesise results was based on the technique of thematic synthesis described by Thomas and Harden. (151) Following multiple readings of the papers to achieve immersion, text was manually coded and extracted, from which subthemes were developed until no further subthemes could be identified. This process was verified with two members of the advisory team who independently read all papers and then reviewed, extracted, coded text and subthemes to confirm comprehensiveness and reliability of the findings (152). Descriptive and draft analytic themes were subsequently developed, presented to, and discussed with, the advisory team in developing and finalising the new analytic construct. Study characteristics and results were analysed for associations between specific themes and studies.

4.2 Findings

4.2.1 Study selection

The search yielded 6,011 papers, 21 of which met the selection criteria (see Figure 4-1). There were no studies exploring the perspectives of non-medical prescribers.

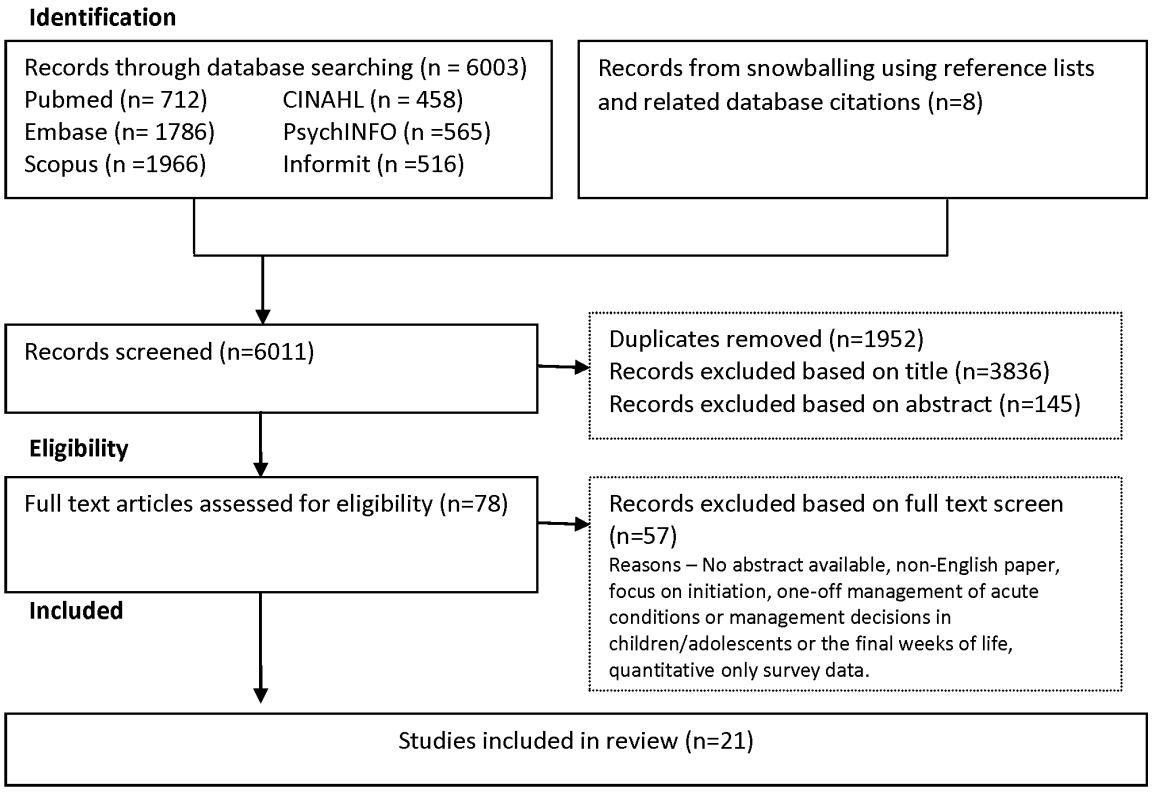


FIGURE 4-1 FLOWCHART OF STUDY SELECTION

4.2.2 Study characteristics

Characteristics of included studies are presented in Table 4-1. All but one, which collected data by survey, used focus groups and semi-structured interviews to collect qualitative data. (153) Four papers explored prescribers' views in relation to multiple medications (i.e. polypharmacy) (154-157) whilst the remaining papers investigated prescribers' views in relation to single PIMs or classes of medications (ten described one or more centrally acting agents such as psychotropics, hypnotics, benzodiazepines, minor opiates and antidepressants(158-167); two for proton pump inhibitors (168, 169) and five for miscellaneous PIMs defined according to pre-specified criteria, a pre-set medication list or clinical judgement. (153, 170-173) Eighteen studies elicited the views of prescribers practising in primary care, (153-165, 168-172) one of prescribers in secondary care,(173) and two of prescribers servicing residential aged care facilities (RACFs). (166, 167)

TABLE 4-1 STUDIES INVESTIGATING THE PERSPECTIVES OF PRESCRIBERS IN VARIOUS SETTINGS

Year of publication	Lead author	Country	Aim	Medication types	Participants & setting	Age focus[a]	Data collection method	Analysis
1995	Britten	England	To identify patients whose current medication is the result of past treatment decisions and is regarded by their current GP as no longer appropriate, and to describe the drugs and the circumstances in which they continue to be prescribed	Miscellaneous PIMs	7 GPs, primary care	All ages	Descriptive survey; GP selected patients prescribed inappropriate medicines, structured data extraction from notes & GP-facilitated interview of patient	N/A
1997	Dybwad	Norway	To understand factors that could result in variations between GPs in order to form hypotheses and build theories about prescribing (main focus on factors that explain higher rates of prescribing)	Benzodiazepines and minor opiates	38 GPs (18 high rate prescribers, 20 medium-to-low rate prescribers), primary care	All ages	SSIs (combined with prescription registration information)	Not stated
1999	Damestoy	Canada	To explore physicians' perceptions and attitudes and the decision-making process associated with prescribing psychotropic medications for elderly patients	Psychotropics (sedatives, hypnotics, anxiolytics and antidepressants)	9 physicians who conduct home visits, primary care	Older patients	(Presumed face-to-face) SSIs	Grounded theory analysis
2000	Cantrill	England & Scotland	To explore factors which may contribute to inappropriate long-term prescribing in United Kingdom general practice	Miscellaneous PIMs	22 GPs, primary care	All ages	Face-to-face & telephone interviews informed by specific examples of PIMs identified by validated indicators	Not stated
2004	Iliffe	England	To explore beliefs and attitudes about continuing or stopping benzodiazepine	Benzodiazepines	72 GPs, primary care	Older patients	Non-standardized interview group discussions	Not stated

Year of publication	Lead author	Country	Aim	Medication types	Participants & setting	Age focus[a]	Data collection method	Analysis
			hypnotics amongst older patients using such medicines, and amongst their general practitioners					
2005	Spinewine	Belgium	To explore the processes leading to inappropriate use of medicines for elderly patients admitted for acute care	Miscellaneous PIMs	3 geriatricians & 2 house officers, hospital elderly acute care wards	Older patients	SSIs with health professionals triangulated with observation on wards and FGs with elderly inpatients	Not stated
2005	Raghunath	England	To understand the prescribing behaviour of GPs by exploring their knowledge, understanding and attitudes towards PPIs	PPIs	49 GPs, primary care	All ages	Focus groups	Not stated
2006	Parr	Australia	To gain more detailed understanding of GP and benzodiazepine user perceptions relating to starting, continuing and stopping benzodiazepine use	Benzodiazepines	28 GPs, primary care	All ages	SSIs	Not stated
2007	Cook	USA	To understand factors influencing chronic use of benzodiazepines in older adults	Benzodiazepines	33 primary care physicians	Older patients	Face-to-face and telephone SSIs	Narrative analysis
2007	Rogers	England	To explore the dilemma the controversial benzodiazepine legacy has created for recent practitioners & their view of prescribing benzodiazepines	Benzodiazepines	22 GPs, primary care	All ages	SSIs	Not stated
2010	Anthierens	Belgium	To describe GPs' views and beliefs on polypharmacy in order to identify the role of the GP in improving prescribing behaviour	Polypharmacy	65 GPs, primary care	Older patients	Face-to-face individual SSIs (literature informed interview guide)	Content analysis

Year of publication	Lead author	Country	Aim	Medication types	Participants & setting	Age focus[a]	Data collection method	Analysis
2010	Dickinson	United Kingdom	To explore the attitudes of older patients and their GPs to chronic prescribing of antidepressant therapy, and factors influencing such prescribing	Antidepressants	10 GPs, primary care	Older patients	SSIs	Framework analysis
2010	Frich	Norway	To explore GPs' and tutors' experiences with peer group academic detailing, and to explore GPs' reasons for deviating from recommended prescribing practice	Miscellaneous PIMs	20 GPs (39 GPs also interviewed on topics outside scope of this review)	Older patients	Focus group interviews following individual receipt of prescription profile report	Thematic content analysis
2010	Moen	Sweden	To explore GPs' perspectives of treating older users of multiple medicines	Polypharmacy	31 GPs (4 private, 27 county-employed), primary care	Older patients	Focus groups (literature informed question guide)	Conventional content analysis
2010	Subelj	Slovenia	To investigate how high-prescribing family physicians explain their own prescription	Benzodiazepines	10 family physicians (5 high and 5 low prescribers), primary care	All ages	SSIs	Not stated
2011	Fried	USA	To explore clinicians' perspectives of and experiences with therapeutic decision making for older persons with multiple medical conditions	Polypharmacy	36 physicians, primary care, Vet affairs and academia	Older patients	Focus groups	Content analysis
2011	Iden	Norway	To explore decision-making among doctors and nurses on antidepressant treatment in nursing homes	Antidepressants	16 doctors, 8 each working full & part time in residential aged care facilities	Older patients	Focus groups	Systematic text condensation & analysis
2012	Flick	Germany	To explore, given the specific risks and the limited effect of	Hypnotics	20 doctors servicing	Older patients	Episodic interviews	Thematic analysis

Year of publication	Lead author	Country	Aim	Medication types	Participants & setting	Age focus[a]	Data collection method	Analysis
			sleeping medication, why doctors prescribe hypnotics for the elderly in long-term care settings		residential aged care facilities			
2012	Schuling	The Netherlands	To explore how experienced GPs feel about deprescribing medication in older patients with multimorbidity and to what extent they involve patients in these decisions	Polypharmacy	29 GPs, primary care	Older patients	Focus groups	Not stated
2013	Clyne	Ireland	To evaluate GP perspectives on a pilot intervention (to reduce PIP in Irish primary care)	Miscellaneous PIMs	8 GPs in focus group & 5 GPs for SSIs, primary care	Older patients	Focus group & SSIs	Thematic analysis
2013	Wermeling	Germany	To describe factors and motives associated with the inappropriate continuation of prescriptions of PPIs in primary care	PPIs	10 GPs (5 who frequently continue and 5 who frequently discontinue PPIs), primary care	All ages	SSIs	Framework analysis

GPs = General Practitioners; PIMs = Potentially inappropriate medications; PIP = Potentially inappropriate prescribing; PPIs = Proton Pump Inhibitors; SSIs = Semi-structured interviews.

[a] Age focus refers to the indicative age group of patients who were the focus of participant discussions, as suggested by the terms used in each article, which did not specify exact age ranges.

TABLE 4-2 COMPREHENSIVENESS OF REPORTING ASSESSMENT (COREQ CHECKLIST)

Reporting Criteria	Number N=x of 21	References of studies reporting each criterion
DOMAIN 1:		
Characteristics of research team		
Interviewer/facilitator identified	14	(154-158, 161, 162, 166, 168-173)
Credentials	12	(153, 154, 157-159, 162-164, 166, 170, 171, 173)
Occupation	7	(158, 162-164, 166, 170, 173)
Gender	16	(154-159, 161-163, 166, 167, 169-173)
Experience and training	2	(162, 163)
Relationship with participants		
Relationship established before study started	5	(158, 160, 165, 168, 169)
Participant knowledge of the interviewer	3	(158, 160, 165)
Interviewer characteristics	4	(162, 163, 166, 171)
DOMAIN 2:		
Study design		
Methodological theory identified	15	(154, 156-159, 161, 162, 164, 166-169, 171-173)
Participant selection		
Sampling method (e.g. purposive, convenience)	21	(153-173)
Method of approach	13	(154, 156, 158, 161, 162, 164-167, 169-171, 173)
Sample size	21	(153-173)
Number/reasons for non-participation	7	(156, 158, 159, 161, 164, 165, 168)
Setting		
Setting of data collection	11	(153-156, 158, 160, 161, 163, 165, 169, 170)
Presence of non-participants	0	-
Description of sample	17	(153-158, 161-169, 171, 173)
Data collection		
Interview guide	16	(153-159, 161, 162, 164-167, 170, 171, 173)
Repeat interviews	0	-
Audio/visual recording	19	(154-159, 161-173)
Field notes	6	(154, 156, 161, 164, 166, 171)
Duration	12	(154, 155, 157, 159, 161, 165-169, 172, 173)
Data saturation	7	(154, 155, 159, 161-163, 168)
Transcripts returned to participants	1	(168)
DOMAIN 3		
Data analysis		
Number of data coders	16	(154-158, 160, 161, 163-166, 168-171, 173)
Description of coding tree	15	(154-158, 161, 163-169, 171, 173)
Derivation of themes	18	(154-158, 160-171, 173)
Software	6	(154, 162, 164, 168, 172, 173)
Participant checking	2	(161, 173)
Reporting		
Participant quotations presented	18	(154-158, 161-173)
Data and findings consistent	20	(153-159, 161-173)
Clarity of major themes	18	(153-158, 161-171, 173)
Clarity of minor themes	14	(153-155, 157, 158, 160, 161, 163-165, 167-169, 173)

4.2.3 COREQ assessment

The completeness of reporting varied across studies, with an average of 17 (range 8-22) of 32 items from the COREQ checklist clearly documented, see Table 4-2. The single descriptive survey reported nine of 24 applicable fields. (153) See Appendix 5 for the completed COREQ assessment for each study.

Lowest rates of reporting were observed in Domain 1 meaning that researcher bias (poor confirmability) cannot be excluded. (150) Greater transparency was apparent with Domains 2 and 3 allowing comparatively better assessment of the credibility, dependability and transferability of study findings. For example, all studies reported the sample size and method and most reported a description of the sample and interview guide. There was consistency between raw data and interpretive findings in all papers except one in which the interpretation was so brief that its accuracy was considered doubtful. (160) For five papers it was unclear whether ethics approval was obtained. (153, 158, 167, 168, 170)

4.2.4 Synthesis of findings

Thematic synthesis yielded 42 subthemes, 12 unique descriptive themes and four analytic themes (see Figure 4-2), with multiple interdependencies and relationships. Barrier and enabler descriptive themes and subthemes tended to mirror each other for each analytic theme of awareness, inertia, self-efficacy and feasibility. The first three themes reflect factors intrinsic to the prescriber and his/her decision-making process while the fourth deals with extrinsic factors. Table 4-3 and Table 4-4 provide illustrative quotations from either primary study participants or study authors relating to barrier and enabler subthemes, respectively.

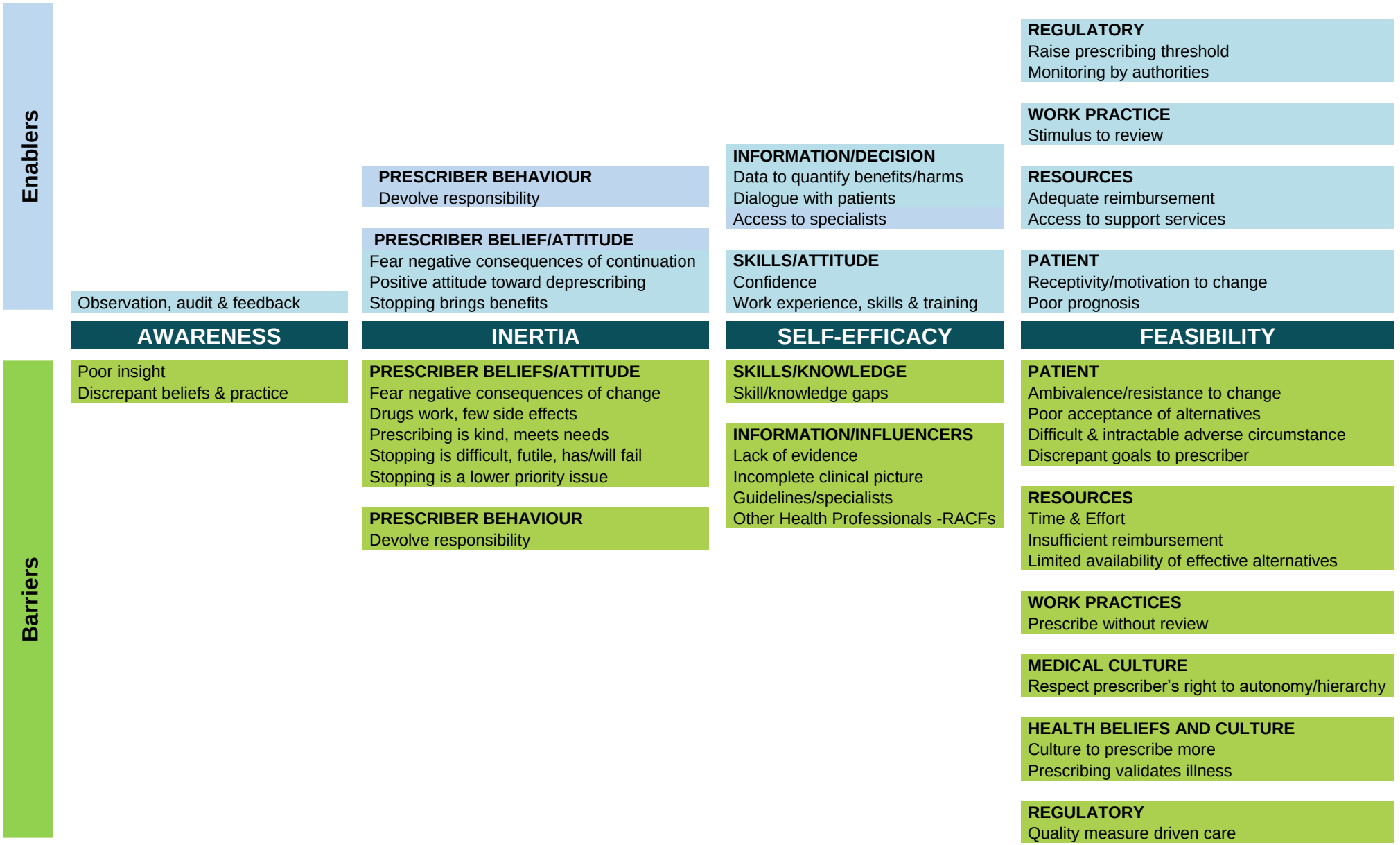


FIGURE 4-2 SCHEMATIC REPRESENTATION OF BARRIERS AND ENABLERS ASSOCIATED WITH EACH ANALYTIC AND DESCRIPTIVE THEME

TABLE 4-3 ILLUSTRATIVE QUOTATIONS FOR BARRIER THEMES AND SUBTHEMES

Analytic & Descriptive themes	Subtheme and References	Characteristics of studies from which subthemes were derived: Type of PIMs; Age focus[a]; Setting (number of references).	Illustrative quotations "*Italicised text*" = Primary quote (i.e. quote from a study participant from an included paper) 'Non-italicised text' = Secondary quote (i.e. quote from study authors' findings from an included paper)
AWARENESS			
	Poor insight (170, 171, 173)	Misc PIMs (3); Older (2) & all ages (1); Primary (2) & secondary care (1).	"*When I saw the list of patients [to be discussed with the researcher], I was quite happy about the prescriptions…but obviously when you look at them in more detail there are anomalies there that ought to be either checked on, reviewed or even altered."* (170)
	Discrepant beliefs and practice (155, 158, 162, 165, 168)	Benzos (2) & minor opiates (1), Polypharm (1), PPIs (1); Older (1) & all ages (4); Primary care (5).	'In contrast to stated beliefs about best practice, physicians estimated that 5-10% of their older adult patients were using benzodiazepines on a daily basis for at least the past 3 months.' (162)
INERTIA			
PRESCRIBER BELIEFs/ ATTITUDE	Fear of unknown/negative consequences of change (for the prescriber, patient and staff) (153-155, 158-160, 162, 164, 166-171, 173)	Antidepressants (2), Benzos (2) & minor opiates (1), Hypnotics (1), Misc PIMs (4), Polypharm (2), PPIs (2), Psychotropics (1); Older (9) & all ages (6); Primary (12), residential aged (2) & secondary (1) care.	*"He gets very worried and excitable if you attempt to change anything… even just something minor would cause him virtually a breakdown."* (170) *"We can't predict the effect [of deprescribing] for the individual patient."* (155) "*It's scary to stop a medication that's been going for a long time, because you kind of think am I opening a can of worms here, because I don't know what the reasons were for them starting that medication. To explore all that will take, you know, I can't do all that now, I will have to do that another time."* (164) *"I suggest to them that ideally we should try to get them off of that, but if they're saying, been there, done that, that didn't work for me when I came off of this, I don't think it's worth getting into a big knock-down drag-out [fight] with them or having them leave my practice over this issue".* (162)
	Drugs work, few side effects (158, 159, 162, 163, 165, 167-169, 171)	Benzos (3) & minor opiates (1), Hypnotics (1), Misc PIMs (1), PPIs (2), Psychotropics (1); Older (4) & all ages (5); Primary (8) & residential aged (1) care.	'In their [the physicians'] view psychotropic medication helps the elderly patient remain functional and is the least problematic solution... The physicians stated that they often do not see side effects and that patients often do not report them...' (159)

	Prescribing is kind, meets needs (of patient, staff, carer) (158, 161-165, 167, 168)	Antidepressants (1), Benzos (4) & minor opiates (1), Hypnotics (1), PPIs (1); Older (3) & all ages (5); Primary (7) & residential aged (1) care.	*"There is a paradox concerning older patients. You do not want to make them grow dull, but on the other hand you know their chronic problems, and you know that at their age the drugs are not so addictive. You want them to keep their minds clear, but on the other hand I do have a tendency to be permissive to older patients."* (158) *"...It treats our own pain as well as our patients' pain, 'cos we want to help people and make people feel better. So if we give people something and make them feel better, then everybody seems to be happier."* (163)
	Stopping is difficult, futile has/will fail (155, 158, 160-162, 166, 167, 170, 171) ,	Antidepressants (1), Benzos (3) & minor opiates (1), Hypnotics (1), Polypharm (1), Misc PIMs (2); Older (6) & all ages (3); Primary (7) & residential aged (2) care.	*"Let's pretend it's an octogenarian...if it's gonna make the patient feel better, I don't care if the patient's on it for the rest of their life."* (162) 'Most frequent concern identified was the difficulty anticipated in persuading older patients to withdraw after years of using benzodiazepines.' (160) *"In my experience, patients get hooked on PPIs, it is almost addictive like heroin and people appear to experience severe indigestion symptoms on attempting to stop them."* (168)
	Stopping is a lower priority issue (162, 164, 168, 169, 173)	Antidepressants (1), Benzos (1), Misc PIMs (1), PPIs (2); Older (3) & all ages (2); Primary (4) & secondary (1) care.	"... We are always faced with multiple problems and PPIs are just one issue..." (168)
PRESCRIBER BEHAVIOUR	Devolve responsibility (153, 158, 159, 164-167, 173)	Antidepressants (2), Benzos (1) & minor opiates (1), Hypnotics (1), Misc PIMs (2), Psychotropics (1); Older (5) & all ages (3); Primary (5), secondary (1) & residential aged (2) care.	'They [the physicians] recognized that the inappropriate use of psychotropic medication for elderly patients was a public health problem, but they felt that it was beyond the scope of the individual physician.' (159) *"(...) I ask them if it should be a sleeping pill or another of the available options and mostly they have a need for sleeping pills."* (167) *"I have been running this practice for twelve years. I took it over from an older colleague. I took over all his patients. They were mostly old people. Prescribing policy has been rather liberal, and I have continued this policy."* (158)

SELF-EFFICACY			
SKILLS/ KNOWLEDGE	Skills/knowledge gaps (154-159, 164, 169, 173)	Antidepressants (1), Benzos & minor opiates (1), Misc PIMs (1), Polypharm (4), PPIs (1), Psychotropics (1); Older (7) & all ages (2); Primary (8) & secondary (1) care.	*“I don’t have enough time for education about the newest information on psychiatric disorders, and better communication with specialists would be very helpful.” (165)* ‘Side effects are not always recognised as such.’ (156) "*When house officers come on our ward, they haven't necessarily been trained in geriatrics. So they arrive here, and then they start with 10mg of morphine every four hours. That's too much*." (Hospital based geriatrician) (173) *"You look at the medication list and want to reduce it but then you can't find things you can eliminate."* (155)
INFORMATION/ INFLUENCERS	Lack of evidence (154, 155, 157)	Polypharm (3); Older age (3); Primary care (3).	*“To me, the guidelines are kind of a hindrance. At the moment they do not cater for older patients”* (155)
	Incomplete clinical picture (154-157, 164, 165, 170, 171, 173)	Antidepressants (1), Benzos (1), Misc PIMs (3), Polypharm (4); Older (7) & all ages (2); Primary (8) & secondary (1) care.	*"The problem is that the medication lists of the doctors involved are not exchanged and are consequently inconsistent."* (155) *"One has discovered that they might have completely different expectations than what the doctor had from the beginning. Do they want to survive for five more years or? And so on. What are their expectations?"* (154) ‘…Medicines, (mainly for chronic conditions) were sometimes not appropriately reviewed because there was no written information on indication and follow-up or because this was not readily available.’ (173) "...sometimes the older people decide for themselves to reduce some of their medication or to adjust the doses without telling their GP. Therefore as their GP you can have the wrong impression about their medication intake..." (156)
	Guidelines/specialists (154-157, 162, 168, 170, 173)	Benzos (1), Misc PIMs (2), Polypharm (4), PPIs (1); Older (6) & all ages (2); Primary (7) & secondary (1) care.	‘When existing guidelines are debated, GPs felt deceived and insecure... The importance of individualising treatment was also expressed and many guidelines were perceived as too rigid leading to a standardized 'kit' of medicines per indication...’ (154) *“I have difficulty not following the guidelines if I don't have good reasons to do so."* (155)

			"When the hospital consultant recommends a treatment it's difficult… for us not to prescribe unless there is a very good reason. To some extent we feel obliged to carry on when they have initiated it." (170)
	Other Health Professionals (Aged Care) (166, 167)	Antidepressants (1) & Hypnotics (1); Older patients (2); Aged care (2).	*"(…) in such a situation it amounts to the sleeping pill, because everybody else's need is the sleeping pill, and I would have to fight tooth and nail if really I wanted to avoid this."* (167) *"They (RACF nurses) called me on the carpet to tell me that withdrawing antidepressants was not a clever thing to do because the patient became angrier and resisted care. They therefore demanded that I reinstate medication."* (166)
FEASIBILITY			
PATIENT	Ambivalence/resistance to change (153-156, 159, 161, 162, 164, 167, 168, 170, 172, 173)	Antidepressants (2), Benzos (2), Hypnotics (1), Misc PIMs (4), Polypharm (3), PPIs (1), Psychotropics (1); Older (9) & all ages (4); Primary (11), secondary (1) & residential aged (1) care.	*"When I said initially we wanted her to come off it, she said, oh no, I've been on that for ages, and I don't want to come off it."* (172) *"The discontent rarely lies with the patient themselves."* (155)
	Poor acceptance of alternatives (161, 162, 166-168)	Antidepressants (1), Benzos (2), Hypnotics (1), PPIs (1); Older (3) & all ages (2); Primary (3) & residential aged (2) care.	*"... these types of people and they tend not to want to help themselves, you know they won't take the hypnotherapy and they won't go to yoga classes and they won't do anything else. They just want a quick fix."* (161)
	Difficult & intractable adverse circumstance (158, 159, 161, 163, 164)	Antidepressants (1), Benzos (2) & minor opiates (1), Psychotropics (1); Older (2) & all ages (3); Primary care (5).	*"I think they have horrible lives, a lot of them… I think it's a combination of all things, their health, their social circumstances… I think a lot of people are on antidepressants because of everything put together. And you can't… change most of the factors that cause it."* (164)
	Discrepant goals to prescriber (154, 157)	Polypharmacy (2); Older age (2); Primary care (2).	*"I kind of get aggravated that half of the medicines that I think are totally rubbish are the ones that the patient really wants to take."* (157)
RESOURCES	Time and effort (154, 157, 158, 161, 162, 164-166, 170, 172, 173)	Antidepressants (2), Benzos (3) & minor opiates (1), Misc PIMs (3), Polypharm (2); Older (7) & all ages (4); Primary (9), secondary (1) & residential aged (1) care.	*"We have a big problem with long-term hypnotic use. It would take an awful lot of work and it's purely a time and work problem".* (170)

	Insufficient reimbursement (161, 162)	Benzos (2); Older (1) & all ages (1); Primary (2) care.	'… a lack time or resources to provide counselling, especially due to the absence of remuneration for doing so.' (161)
	Limited availability of effective alternatives (161, 162, 165-167)	Antidepressants (1), Benzos (3), Hypnotics (1); Older (3) & all ages (2); Primary (3) & residential aged (2) care.	'...There is hardly any alternative to medicamentous therapy.' (167)
WORK PRACTICES	Prescribe without review (158, 159, 166, 167, 169-171)	Antidepressants (1), Benzos & minor opiates (1), Hypnotics (1), Misc PIMs (2), PPIs (1), Psychotropics (1); Older (4) & all ages (3); Primary (5) & residential aged (2) care.	*"(...) then he gets something and he continues this pill, and then the issue is over for him, then it's quiet, and then he has his pill and then he sleeps through, and from time to time you may enquire, it if occurs to you while looking at his medication."* (167)*"When we work in a large health centre, then we sign prescriptions for each other... when a colleague is absent, we issue prescriptions for him that day. Any prescription I issue is my responsibility, but if you are asked to prescribe a particular drug [for a colleague] then you sign it in the reception. I don't check which other drugs that person uses."* (171)
MEDICAL CULTURE	Respect prescriber's right to autonomy & hierarchy (153, 154, 158, 161, 169, 170, 173)	Benzos (1) & minor opiates (1), Misc PIMs (3), Polypharm (1), PPIs (1); Older (2) & all ages (5); Primary (6) & secondary (1) care.	'The GPs rarely contact colleagues, for example, hospital specialists, as there is a perceived lack of routines for this as well as an informal understanding not to pursue colleagues' motivations for prescriptions. ' (154)
HEALTH BELIEFS & CULTURE	Culture to prescribe more (156, 166, 171)	Antidepressants (1), Misc PIMs (1), Polypharm (1); Older patients (3), Primary (2) & residential aged (1) care.	*"The number of medications grows slowly. There is a complaint, we give new medication, it continues without really stopping it after a while… and it is our responsibility to try and withdraw it from the patient"* (156)
	Prescribing validates illness (158, 164, 167)	Antidepressants (1), Benzos & minor opiates (1), Hypnotics (1); Older (2) & all ages (1); Primary (2) & residential aged (1) care.	*"They feel that unless they are on a tablet for it then they are not having any treatment. There are a lot of those kinds of people."* (164)
REGULATORY	Quality measure driven care (157)	Polypharm (1); Older (1); Primary care (1).	*"Another factor that we experience at the VA is these electronic reminders that tell you to do things…What I do really depends on who is in front of me…So the reminder comes up and it makes no sense. This guy's LDL is 101.8… Should I go from 40 to 80 of simvastatin? And what's the risk and benefit there?"* (157)

Benzos = Benzodiazepines; Misc = Miscellaneous, PIMs = Potentially inappropriate medications; Polypharm = Polypharmacy, PPIs = Proton Pump Inhibitors.[a] Age range refers to the indicative age group of patients who were the focus of participant discussions, as suggested by the terms used in each article, which did not specify exact age ranges.

TABLE 4-4 ILLUSTRATIVE QUOTATIONS FOR ENABLER THEMES AND SUBTHEMES

Analytic & Descriptive themes	Subtheme	Characteristics of studies from which subthemes were derived including: Type of PIMs; Age focus[a]; Setting (number of references).	Illustrative quotations "*Italicised text*" = Primary quote (i.e. quote from a study participant from an included paper) 'Non-italicised text' = Secondary quote (i.e. quote from study authors' findings from an included paper)
AWARENESS			
	Review, observation, audit & feedback (170, 171, 173)	Misc PIMs (3); Older (2) & all ages (1); Primary (2) & secondary (1) care.	As above.(170)
INERTIA			
PRESCRIBER BELIEFs/ATTITUDE	Fear of negative/unknown consequences of continuation (168)	PPIs (1); All ages (1); Primary care (1).	*"Miracle all right, but too good of anything can be dangerous. Would just like to reiterate that, let me say they [PPIs] even work too well, what worries me is won't there be long-term missed cancers?"* (168)
	Positive attitude toward deprescribing (155)	Polypharm (1); Older age (1); Primary care (1).	*"You can have a field day with crossing off medication: 'sure, scrap half of it'."* (155)
	Stopping brings benefits (160, 161, 172)	Benzos (2) & Misc PIMs (1); Older (2) & all ages (1); Primary care (3).	*"O ya, and she was delighted, I stopped some of her other medications because she was in front of me and I had a bit of time to do it."* (172)
PRESCRIBER BEHAVIOUR	Devolve responsibility (153, 164, 168)	Antidepressants (1), Misc PIMs (1), PPIs (1); Older (1) & all ages (2); Primary care (1).	'Some [GPs] preferred to wait until the patient went to hospital where they would be taken off their drugs without the GP being blamed. The GP might even write and ask a hospital doctor to do this.' (153) *"Why not be honest and say, the NHS can't afford to keep giving you these drugs unless there's a very good reason. The patients understand that, and in this day and age they understand perfectly well about cost."* (168)
SELF-EFFICACY			
SKILLS/ ATTITUDE	Confidence (to stop therapy/deviate from guidelines) (157, 169)	Polypharm (1), PPIs (1); Older patients (1) & all ages (1); Primary care (2).	*"It's not as if the life of the patient is suddenly at risk because I take away a pill, yes. [...] in the worst-case heartburn may re-occur or there is upper abdominal discomfort, but that will not immediately cause a bleeding ulcer."* (169)

			"I sort of you know tone those goals down. I am not looking for a Hemaglobin A1C of 7 anymore…so I take the pressure off them and I start removing those medications especially the ones that cause hypoglycaemia." (157)
	Work experience, skills & training (154, 169, 173)	Misc PIMs (1), Polypharm (1), PPIs (1); Older (2) & all ages (1); Primary (2) & secondary (1) care.	*"Yes, maybe problem oriented when you are new. Maybe now one thinks more about consequences, in another way."* (154)
INFORMATION/ DECISION SUPPORT	Data to quantify benefits/harms (154-156, 172)	Misc PIMs (1), Polypharm (3); Older (4); Primary care (4).	*"…because actually what you could do is to give him (patient) some more 'hard core' facts like: 'If you refrain from treatment your chance of stroke is 20%..."* (154)
	Dialogue with patients (153, 154, 168, 170)	Misc PIMs (2), Polypharm (1), PPIs (1); Older (1) & all ages (3); Primary care (4).	'Discussion during the research interview made some patients more willing to consider a change in medication.' (153) 'Adequate discussion with patients was widely recognised as one of the keys to influencing change, but although practiced by some GPs it was not always successful.' (170)
	Access to specialists (164, 165, 168, 173)	Antidepressants (1), Benzos (1), Misc PIMs (1), PPIs (1); Older (2) & all ages (2); Primary (3) & secondary (1) care.	'They (low benzodiazepine prescribing family physicians) desired better cooperation and clear instructions from psychiatrists.' (165)
FEASIBILITY			
PATIENT	Receptivity/motivation to change (157, 161, 170)	Benzos (1), Misc PIMs (1), Polypharm (1); Older (1) & all ages (2); Primary care (3).	*"He's fairly amenable to tinkering with his pills, so we'll look at that".* (170)
	Poor prognosis (173)	Misc PIMs (1); Older age (1); Secondary care (1).	*"Sometimes people have taken 10 medicines while they were in curative care, and gradually they move on to palliative care. Then we must reconsider all the prescriptions, drug by drug, saying: OK, what's the goal? To improve your comfort? Well, this medicine will make you feel more comfortable; we can stop this other one."* (173)
RESOURCES	Adequate reimbursement (162)	Benzos (1); Older age (1); Primary care (1).	*"Reimbursement is very low... I think if it was something that we did get reimbursed on I think you would see physicians' attitudes a lot different. You'd be more willing to spend time." (162)*

	Access to support services (155, 161, 165, 170)	Benzos (2), Polypharm (1), Misc PIMs (1); Older (1) & all ages (3); Primary care (4).	'Most GPs work closely with a local pharmacist [when undertaking medication review to stop medicines]: the task perception of such pharmacists was an important factor when a GP was looking for decision support in medication review' (155)
WORK PRACTICE	Stimulus to review (153, 155, 164, 168, 172, 173)	Antidepressants (1), Misc PIMs (3); Polypharm (1), PPIs (1); Older (4) & all ages (2); Primary (5) & secondary (1) care.	'A new patient entering the practice list is welcomed as an opportunity to review their medication.' (155)
REGULATORY	Raise prescribing threshold (168, 169)	PPIs (2); All ages (2); Primary care (2)	*"I think we are all sitting here and debating about this mainly because of the pressure on us by our pharmaceutical advisors not to prescribe PPIs because of cost implications to the NHS; I bet that this will not be an important topic in 2 years when Losec goes generic."* (168)
	Monitoring by authorities (158)	Benzos & minor opiates (1); All ages (1); Primary care (1).	'The continuous monitoring of prescriptions by health authorities also put stress on the doctors...' (158)

Benzos = Benzodiazepines; Misc = Miscellaneous, PIMs = Potentially inappropriate medications; Polypharm = Polypharmacy, PPIs = Proton Pump Inhibitors. [a]Age focus refers to the indicative age group of patients who were the focus of participant discussions, as suggested by the terms used in each article, which did not specify exact age ranges.

Fewer enablers were reported than barriers and there was variation in the relative contribution of each study to each theme.

4.2.4.1 Awareness

The theme of awareness was apparent in the three papers which utilised audit or informal third-party (e.g. other health professional) observation and feedback. (170, 171, 173) Poor insight was an observed rather than reported barrier, with interventions to raise prescriber awareness an enabler to minimising the prescription of PIMs. Prescriber beliefs at a population level did not necessarily translate to prescribing practices at an individual level. For example, agreement among prescribers that benzodiazepines should not be used regularly or long-term did not necessarily preclude such prescribing in individual patients. (158, 162, 165)

4.2.4.2 Inertia

Inertia was defined as failure to act, despite awareness that prescribing is potentially inappropriate, because ceasing PIMs was perceived to be a lower value proposition than continuing PIMs.

Fear of unknown/negative consequences of change featured in 15 of 22 papers, and related to consequences for: the prescriber (threatened therapeutic relationship, diminished credibility, increased initial and ongoing workload, potential for litigation, conflict with other prescribers/health professionals); (153-155, 158-160, 162, 164, 167-171, 173) the patient (withdrawal syndrome, symptom relapse or increased risk of the condition/event for which preventive medication was originally prescribed); (160, 162, 164, 166-171) and other health professionals (increased workload and safety concerns of staff in RACFs). (166, 167) The prescriber beliefs that facilitate cessation were the converse, that is, fear of unknown/negative consequences of continuation,(168) a positive attitude to stopping medicines (155) and a belief this practice can bring benefits. (160, 161, 172)

The barrier belief that drugs appear to work with few adverse effects was apparent in nine papers (158, 159, 162, 163, 165, 167-169, 171) of which two studied ‘high-rate’ and ‘low-rate’ benzodiazepine prescribers. ‘High-rate’ prescribers consistently downplayed risks of harm, whereas ‘low/ medium-rate’ prescribers were more conscious of such risks. (158, 165) The futility and potential harm of cessation in patients of advanced age was a subtheme

predominantly present in papers considering psychoactive agents. (158, 159, 162, 167, 170, 171)

Another barrier was the devolvement to another party of responsibility for the decision to continue or cease a medication (e.g. another prescriber, health professional, society, or the patient). One example was continuation of PIMs in patients that prescribers had inherited from colleagues where the former failed to question the rationale used by the latter in prescribing such drugs. (153, 158, 165, 173) Another example was the provision of PIMs upon the request of RACF nursing staff (166) or patients (158, 164, 167) without critical prescriber review. Finally, inappropriate prescribing of psychotropics, while viewed as a public health concern, was considered beyond the scope of individual prescribers. (159)

4.2.4.3 Self-efficacy

The analytic theme of self-efficacy refers to factors that influence a prescriber's belief and confidence in his or her ability to address PIM use. It involves subthemes relating to knowledge, skill, attitudes, influences, information and decision support.

Knowledge or skill deficits, (154-159, 164, 169, 173) including difficulty balancing the benefits and harms of therapy, (154-157) recognising adverse drug effects (155, 156) and establishing clear cut diagnoses/indications for medicines (158, 159, 164) were challenges prescribers faced in identifying and managing PIMs. Balancing the benefits and harms was perceived to be especially difficult when reviewing preventive medications in multimorbid older people with polypharmacy where shorter life expectancy, uncertain future benefits and higher susceptibility to more immediate adverse drug effects must all be considered. (154-157) On the other hand, better quantification of the benefits and harms of therapy, (154-156, 172) confidence to deviate from guidelines and stop medications if thought necessary, (157, 169) greater experience, (154, 169) and targeted training, especially in prescribing for older people, (173) were seen as enabling factors.

Compounding generic knowledge and skill gaps were information deficits specific to individual prescribing decisions, resulting from poor communication with multiple prescribers and specialists involved in patient care, inadequate transfer of information at care interfaces, fragmented and difficult-to-access patient medical records, and failure of patients to know/disclose their full medical history/medication lists to prescribers. (154-157, 164, 165,

170, 171, 173) This subtheme linked strongly with demands on prescribers in regards to time and effort, and in two papers was associated with low motivation arising from a perceived inability to efficiently access all information required for optimal prescribing. (164, 173)

Eight papers discussed the influence of care recommendations from guidelines and specialists. (154-157, 162, 168, 170, 173) Guidelines were often viewed negatively, with prescribers feeling pressured to comply with recommendations at odds with the complexities of clinical practice. (154-156, 168, 170) Pressure from staff to continue prescribing PIMs, often to maintain facility routines, was presented as a barrier unique to RACFs. (166, 167) Offsetting this were enablers centred on greater dialogue with patients to increase understanding and facilitate shared decision making,(153, 154, 168, 170) as well as timely access to, and decision support from, specialists, particularly geriatricians and psychiatrists. (161, 164, 165, 168, 170, 173)

4.2.4.4 Feasibility

Feasibility refers to factors, external to the prescriber, which determine the ease or likelihood of change. They relate to patient characteristics, resource availability, work practices, medical and societal health beliefs and culture, and regulations.

The most frequently expressed barrier concerning patients was their ambivalence or resistance to change (153-156, 159, 161, 162, 164, 167, 168, 170, 172, 173) and their poor acceptance of alternative therapies. (161, 162, 166-168) In contrast, receptivity and capacity to change was identified as an enabler in three studies, (157, 161, 170) as was a poor prognosis which helped crystallise care goals and prompt review of the appropriateness of existing drug regimens. (173)

Limited time and effort to review and discontinue medications (154, 157, 158, 161, 162, 164-166, 170, 172, 173) was the most common resource constraint followed by limited availability of effective non-drug treatment options. (159, 161, 162, 165-167) Adequate reimbursement (162) and access to support services such as mental health workers and pharmacists for medication review (155, 161, 165, 170) emerged as enablers.

Certain work practices were raised as barriers to deprescribing, such as provision of repeats for a prescriber's own or colleague's patients, (158, 170, 171) and the absence of explicit treatment plans or formal or scheduled medication review. (158, 167) The mirroring enablers

were opportunities to review medication regimens (e.g. hospital admission,(153, 173) change of prescriber,(155) or specialist(164) or scheduled review). (168, 172)

Remaining descriptive themes related to medical and societal health beliefs, cultural and regulatory factors. The most frequently mentioned were discomfort and reluctance to question a colleague's prescribing decisions (153, 154, 158, 161, 169, 170, 173) associated with respect for professional autonomy or the medical hierarchy when specialist prescribers were involved.

Externally imposed guideline-based quality measures were presented as a barrier to minimising the prescription of PIMs. (157) Raising the prescribing threshold for medications (e.g. through increased cost or restricted access) and monitoring by authorities were seen by prescribers as unwelcome and potentially perverse enablers. (168, 169)

4.3 Discussion

This systematic review comprehensively investigated prescriber barriers and enablers to minimising the prevalence of chronically prescribed PIMs in adults. The thematic construct developed from published literature centred on awareness, inertia, self-efficacy and feasibility. It principally reflects the perspectives of primary care physicians (i.e. GPs) caring for older, community living adults. Although the themes and subthemes have been presented separately, the reasons doctors continue to prescribe, or do not cease, PIMs are multifactorial, highly interdependent and impacted by considerable clinical complexity.

Many subthemes were common to papers regardless of inter-study differences in the PIMs discussed, patient age and clinical setting (e.g. primary, secondary or residential aged care). Subthemes varied according to whether studies focussed on polypharmacy or single PIMs or classes of PIMs, which was also associated with differing levels of prescriber insight and certainty. In the four studies focussed on polypharmacy, prescribers were aware of polypharmacy-related harm but could not easily identify which medications were potentially or actually inappropriate, as reflected by the subthemes 'difficulty/inability to balance benefits and harms of therapy', (154-157) 'inability to recognise adverse drug effects, (155, 156) 'lack of evidence' (154, 155, 157) and 'incomplete clinical picture'. (154-157) In other studies focussing on specific classes of over-prescribed medications, prescribers were aware of this inappropriateness, but in response voiced various rationalisations for continued prescribing

such as ‘drugs work, few adverse effects’, (158, 159, 162, 163, 165, 167-169, 171) ‘prescribing is kind and meets needs’, (158, 161-165, 167, 168) ‘stopping is difficult, futile, has or will fail’, (158, 160-162, 166, 167, 171) ‘poor (patient) acceptance of alternatives’, (161, 162, 166-168) and ‘difficult and intractable adverse (patient) circumstance’. (158, 159, 161, 163, 164)

However, in other studies focussing on miscellaneous PIMs, prescribers were generally not aware of their potential or actual inappropriate prescribing until this was revealed to them (e.g. through audit and feedback). (170, 171, 173)

No definite thematic pattern was observed from the subthemes of six studies which did not specifically focus on the care of older people (153, 161, 163, 165, 168, 169) compared to the remaining 15 which did. Compared to studies in primary care, unique themes emerged from papers set in RACFs and acute care settings. For example, pressure on prescribers to continue prescribing PIMs at the request of RACF nursing staff was unique to this setting. (166, 167) The one study set in acute care highlighted inexperience and training deficiencies of junior prescribers, as assessed by three geriatricians. (173)

The finding that poor insight into potentially inappropriate prescribing practices was only apparent in studies where prescribers were made aware of this is unsurprising, given prescribers do not intentionally prescribe medications inappropriately. It demonstrates the importance of awareness-raising strategies for prescribers. Inertia, as in failure to deprescribe when appropriate, sits at odds with the more traditional use of the word as symbolising failure to intensify therapy when indicated. (174) Inertia has been linked to ‘omission bias’ where individuals deem harm resulting from an act of commission to be worse than that resulting from an act of omission.(175, 176) In the case of deprescribing as an act of commission, it becomes more a matter of reconciling a level of expected utility (accrual of benefits) with a level of acceptable regret (potential to cause some harm). (177) Fear of negative consequences resulting from deprescribing contributes to inertia and is not easily allayed by the current limited evidence base regarding the safety and efficacy of deprescribing. (178) In the same papers in which prescribers rationalised continuation of therapy with the belief that drugs work and have few adverse effects, (158, 159, 162, 163, 165, 167-169, 171) prescribers also identified different thresholds for initiating versus continuing the same

therapy. This anomaly suggests either a lack of prescriber insight, clear differences in prescribers' attitudes toward initiation versus continuation, or a social response bias towards a false belief induced by the methodology used by interviewers.

4.3.1 Relevance to previous literature

One meta-synthesis of seven papers exploring prescribers' perspectives of why potentially inappropriate prescribing (PIP) occurs in older people has recently been published.(179) Compared to the review conducted in this thesis, this more recent study had a generic focus on PIP, including under-prescribing and its search strategy retrieved fewer articles (n= 7). Scanning the reference list did not reveal any additional papers which would have met the selection criteria in the thesis study and therefore would not have yielded any additional themes.

These findings are consistent with the literature (largely focused on *initiation* of therapy) suggesting that pharmacological considerations are not the only factors impacting doctors' prescribing decisions. (120) Rather, prescribing decisions result from interacting clinical, social and cultural factors impacting on both the patient and prescriber. (120-122)

Reeve *et al* published a review of patient barriers and enablers to deprescribing (8) and emphasised the importance of a patient-centred deprescribing process.(50) When comparing their findings with those from the thesis study, prescribers' barriers are concordant with those of patients with respect to resistance to change, poor acceptance of non-drug alternatives, and fear of negative consequences of discontinuation. However, prescribers also underestimate enabling factors including patients' experiences/concerns of adverse effects, dislike of multiple medicines, and being assured that a ceased medication can be recommenced if necessary. Patients also reported their GP could be highly influential in encouraging them to discontinue therapy, a perception not echoed amongst prescribers. (8) Prescribers need to discuss, rather than assume, patient attitudes towards their medicines and to deprescribing, in the context of their current care goals.

Previous reviews of interventions to change prescribing behaviour have found that active and multifaceted interventions targeting a range of barriers to change are more likely to be effective than single, passive interventions. (129, 130) The findings from this systematic review appear to support this, but further research is required to identify the barriers and

enablers with the greatest potential for impact when designing targeted deprescribing interventions for a given care setting.

4.3.2 Strengths and limitations

Inconsistent terminology and poor indexing of search terms relating to deprescribing and inappropriate therapy greatly hampered ability to identify relevant studies. In this case, the mitigation efforts comprised a comprehensive pre-scoping exercise, a highly iterative search strategy tailored to each database, and snowballing from reference lists and related citations.

Despite no search restrictions on patient age, clinical setting, or type of PIM, most study participants were experienced GPs/primary care physicians caring for older, community living adults. Caution is therefore needed when generalising the findings from the systematic review conducted for this thesis to other settings or patient groups. However, two recent cross-sectional studies looking at barriers to discontinuation of benzodiazepines and antipsychotics in nursing homes reflected subthemes identified in this review - fear of negative consequences of discontinuation such as poorer quality of life, symptom recurrence, greater workload and a lack of available, effective, non-drug alternatives. (180, 181)

Many of the papers focussed on relatively few drug classes (psychotropics and PPIs) and only four focussed on polypharmacy. Although some subthemes were common to all types of studies (single and miscellaneous PIMs and polypharmacy papers), others were not. It is possible that, had more medication classes been studied, some of this review's findings may have been different.

The strengths of the review included adherence to a peer-reviewed, documented methodology for thematic synthesis, COREQ assessment of studies allowing assessment of potential for bias, compliance with ENTREQ reporting requirements and a multi-disciplinary team of investigators to validate theme identification and synthesis.

4.4 Relevant studies published since 2014

Since the publication of the systematic review in 2014, 11 original research papers meeting the eligibility criteria have been published, the study characteristics and key findings of which have been summarised in Table 4-5 and Table 4-6, respectively. To identify these studies, the original search strategy (i.e. searching all five databases and snowballing from reference lists) and the process for study selection was repeated. Again, these studies principally investigated GPs' views regarding the management of older adults in the primary care setting, although there was a higher proportion of studies eliciting prescribers' views on polypharmacy. That is, six papers explored prescribers' views in relation to polypharmacy (182-187), and the remaining papers investigated prescribers' views in relation to classes of PIMs [two papers on preventive cardiovascular medications (188, 189), two on a range of PIMs (190, 191), and one exclusively on anticholinergic and sedative medications (192)]. All but one study (185), based on data collected using the nominal group technique, involved focus groups or semi-structured interviews to collect qualitative data. Six papers elicited views of prescribers' practising exclusively in primary care (183, 186, 188-191), two of prescribers' practising in primary care and the hospital setting (187, 192), and three papers of prescribers' practising in residential aged.(182, 184, 185)

Analysis and synthesis of key findings from these papers resulted in very minor changes to the barriers/enablers published in the systematic review and no change to the overarching themes or conceptual framework. The minor changes reflect the PIMs examined and the practice setting. For example, studies by Ailabouni *et al* (182) and Palagyi *et al (184)*, which elicited residential aged care prescribers' perspectives, described more barriers pertaining to the regulatory and organisational factors of residential aged care, such as policies, work practices and/or resources (including staff and IT platform limitations). Similarly, the papers reporting prescribers' perspectives from the residential aged care and hospital settings, where patients tend to be sicker, noted more barriers to patient engagement and agency, such as impairments affecting communication or an inability to cope with change.(182, 184, 185, 187)

There was a greater emphasis on factors pertaining to the fragmentation of care, the need for better inter-professional relationships and communication and the desire for more team-based approaches to care. (183, 186, 187, 192) This finding is potentially the consequence of the

higher proportion of papers in more recent times investigating prescribers' views on polypharmacy (involving multiple prescribers and health care practitioners across settings), rather than earlier published papers which tended to focus on individual classes of PIMs.

TABLE 4-5 STUDIES REPORTING PRESCRIBERS' BARRIERS AND ENABLERS TO MINIMISING PIM SINCE DECEMBER 2014

Year of publication	Lead author	Country	Aim[a]	Medication types	Participants & setting	Age focus[b]	Data collection method	Analysis
2015	Magin	Australia	To explore the prescribing, and the rationale for this prescribing, of PIMs in older persons by Australian GPs	Miscellaneous PIMs	22 GPs, primary care	Older patients	SSIs	Thematic analysis
2016	Ailabouni	New Zealand	To investigate GPs' perceived challenges to deprescribing in residential care and possible enablers supporting GPs implement deprescribing	Polypharmacy	10 GPs, residential aged care	Older patients	SSIs	Thematic analysis using TDF
2016	Clyne	Ireland	To explore qualitatively, GP perspectives regarding prescribing and PIP in older primary care patients	Polypharmacy	17 GPs, primary care	Older patients	SSIs	Thematic analysis
2016	Kouladjian	Australia	To investigate perspectives of health care practitioners (HCPs) surrounding deprescribing (withdrawal) of anticholinergic and sedative medications in older adults	Anticholinergic & sedative medications	12 GPs, primary care; 13 specialist physicians [c], hospital setting (also 12 accredited pharmacists, primary care)	Older patients	Focus group discussions and SSIs	Thematic analysis
2016	Luymes[d]	Netherlands	To identify GP (and patients) barriers to and enablers of deprescribing potentially inappropriate	Preventive cardiovascular medications	10 GPs, primary care (also 49 patients but excluded from this analysis)	All adults	Audiotaping consultations between GPs and patients	Content & Framework analysis

Year of publication	Lead author	Country	Aim[a]	Medication types	Participants & setting	Age focus[b]	Data collection method	Analysis
			cardiovascular medication					
2016	Nixon	Denmark	To examine how GPs make decisions about discontinuing medication (Note two other aims were not directly relevant to SR)	Statins	24 GPs, primary care	All adults	SSIs with participant observations	Thematic analysis using Gioia method
2016	Palagyi	Australia	To explore perceptions of medication use and the concept of deprescribing in LTCFs	Polypharmacy	8 GPs, residential aged care (Also 25 LTCF residents, 16 relatives, 19 LTCF staff members)	Older patients	Focus group discussions	Thematic analysis using the Integrative Model of Behaviour Prediction
2016	Turner	Australia	To rank factors that GPs, nurses, pharmacists and residents perceive as most important when deciding whether or not to deprescribe medications	Polypharmacy	19 GPs, residential aged care (also 11 residents/representatives, 12 nurses and 14 pharmacists)	Older patients	Nominal group technique	Nominal group technique
2016	Voigt	Germany	Multiple aims, one of which was to understand family physicians' reasons for prescription of PIMs	Miscellaneous PIMs, with a focus on sedatives/ hypnotics	7 Family Physicians, primary care	Older patients	SSIs	Content analysis
2017	Anderson	Australia	To explore the views of GPs and CPs about inappropriate polypharmacy and the reasoning they apply to deprescribing in primary care, and to	Polypharmacy	32 GPs (and 15 CPs), primary care	Older patients	Focus group discussions	Framework analysis

Year of publication	Lead author	Country	Aim[a]	Medication types	Participants & setting	Age focus[b]	Data collection method	Analysis
			identify factors that support or inhibit this cognitive process					
2017	McNamara	Australia	To explore current approaches to multimorbidity management, and perceived barriers and enablers to deliver appropriate medications management for community dwelling patients with multimorbidity and polypharmacy	Polypharmacy	14 prescribers, from primary care and hospital setting (8 GPs, 3 general internists, 2 geriatricians, 1 clinical pharmacologist (also 12 HCPs)	Older patients	SSIs	Thematic analysis (deductive)

CPs = consultant pharmacists; GPs = general practitioners; LTCFs = long-term care facilities; PIMs = potentially inappropriate medications; PIP = potentially inappropriate prescribing; PPIs = proton pump inhibitors; SSIs = semi-structured interviews, TDF = Theoretical Domains Framework.

[a] Only the aim directly relevant to the systematic review has been described, i.e. other aims of the study were not listed here. [b]Age focus refers to the indicative age group of patients who were the focus of participant discussions, as suggested by the terms used in each article, which did not specify exact age ranges. [c] Specialist physicians consisted of 10 geriatricians, an addiction/pain specialist, a neurologist and an endocrinologist. [d] This study presented an integrated perspective of patients and GPs but only those barriers and enablers relevant to GPs were extracted and presented.

TABLE 4-6 SUBTHEMES FROM STUDIES REPORTING PRESCRIBERS' BARRIERS AND ENABLERS TO MINIMISING PIMS SINCE DECEMBER 2014 AND HOW THEY RELATE TO THE CONCEPTUAL FRAMEWORK

Lead author & Year of publication	**Major themes[a]**	**Relevant overarching theme from systematic review according to major themes/subthemes pertaining to barriers and enablers to minimising PIMs[b,c]**
Magin, 2015	Knowledge and awareness of potential adverse effects of PIMs Harm benefit decisions regarding the use of PIMs The difficulty of ceasing as opposed to initiating PIMs	Awareness (of potential adverse effects of PIMs) Self-efficacy – information (limitations of guidelines); Inertia – prescriber beliefs/attitude (prescribing is kind and meets needs), Self-efficacy (difficulty weighing benefits and harms to inform course of action); Feasibility – organisational factors (e.g. RACF context could facilitate supervised benzodiazepine withdrawal) Self-efficacy – Information (lack of decision support to quantify harms/benefits) Inertia – prescriber beliefs/attitude (stopping has/will fail); prescriber behaviour (defer decision making; devolve responsibility if medication originally specialist initiated. **Feasibility - patient (trust in prescriber).**
Ailabouni, 2016	Problem recognition	Awareness
	Behaviour change factors Prescribing challenges	Inertia – beliefs/attitudes (fear, uncertainty, low confidence, trying to do good). Self-efficacy – knowledge/skills gaps; information/influencers (lack of evidence; incomplete clinical picture, incl. communication at interface of care, role of guidelines/specialists, role of RACF staff). Feasibility – patient/family/care staff (discrepant goals, patient inability to communicate); resources (time, reimbursement), regulatory/organisational factors (nursing home policies).
	Enablers	**Self-efficacy – information/decision support (guidelines, education); confidence (defined as empowerment)** **Feasibility – resources (more time achieved through pharmacist medication review; reimbursement)**
Clyne, 2016	Complexity of prescribing environment Paternalistic doctor-patient relationship Perceived value of PIP concept	Self-efficacy – Influencers (specialists), Information (incomplete clinical picture -framed as fragmentation of care, poor communication between hospital/community) Feasibility – medical culture (professional autonomy and hierarchy (e.g. specialists – framed as GPs feeling pressured to continue medications initiated by other prescribers, especially GPs) Feasibility – medical culture (paternalistic approach); patient (lack of agency and health literacy) Awareness (and acceptance that PIP exists) Inertia – prescriber beliefs/attitude (stopping is futile, has/will fail, prescribing is kind/meets needs – framed in context of continuing long-term benzodiazepine use in older people)

		Self-efficacy – guidelines (limited applicability of PIP guidelines to real-world patients)
Kouladjian, 2016	Barriers: It's not my fault/job Lack of communication Fragmentation of care (hospital and community) External barriers Clinical uncertainty (re: capacity for deprescribing) Patient and/or carer issues Practice-based issues **Enablers:** **Harms from medications** **Collaboration with patients/HCPs** **Triggers of deprescribing**	 Inertia – prescriber behaviour (devolve responsibility) Self-efficacy – Information/influencers (Other health care practitioners, specialists) (Self-efficacy) - Incomplete clinical picture (Self-efficacy) - Information/influences (incomplete clinical picture), Feasibility – medical culture (respect prescribers' right to autonomy and hierarchy) Feasibility – regulatory Inertia – prescriber beliefs/attitude Feasibility – patient/carer Feasibility – resources (time, effort); Self-efficacy (knowledge) **Inertia – Prescriber belief/attitude (negative consequences of continuation of therapy)** **Self-efficacy – decision support; Feasibility – patient (receptivity/motivation to change)** **Contextual (spans awareness, feasibility)**
Luymes, 2016	Appropriateness Fear Process Influences Dislike Other	Prescribing is appropriate – not previously coded – result of analysis of data collection. Awareness - **identification that medication is unnecessary/inappropriate** Feasibility – patient (barrier - poor acceptance of alternatives, e.g. smoking cessation to lower CV risk) Inertia **– prescriber belief/attitude (deprescribing is positive)** Inertia – prescriber belief/attitude (fear) Feasibility – resources (limited time), **work practices (postpone, stepwise approach, follow-up)** Feasibility – patient (context/circumstance; poor acceptance of alternatives) Self-efficacy – information/influences (specialists) **Enabler to inertia – prescriber belief/attitude (deprescribing is positive – framed as dislike of prescribing medicines)** **Enabler to inertia – prescriber belief/attitude (stopping brings benefits)**
Palagyi, 2016	Environmental factors Skills & Abilities Control beliefs & Self-efficacy Attitudes	Feasibility – Organisational factors in LTCF (lack of coordinated care, poor communication with other providers/family, lack of uniform documentation, technology issues, nursing shortages and lack of skilled personnel), work practices (lack of timely review post-hospital discharge), regulatory factors (LTCF policies, RMMR business rules), resources (poor quality RMMRs; time and effort). Self-efficacy – Skills/knowledge gaps (low confidence), information/influencers (unwilling to question specialists) Inertia – fear (negative consequences of deprescribing, medicolegal concerns); Feasibility – perceived patient/relative expectations

		Inertia – low motivation/apathy due to lack of support; linked to Feasibility – resources (insufficient reimbursement), patient/relative expectations (which are often unrealistic).
Turner, 2016	Evidence for deprescribing Communication with resident/family & resident willingness to deprescribe Health system structure – adequacy of medical & medication history and funding for service Fear of deterioration	Self-efficacy – Information (evidence for deprescribing) Feasibility – patient/carer (capacity to communicate; attitude to change) Feasibility – resources (adequate reimbursement); (Self-efficacy)- information (incomplete clinical picture) Inertia – prescriber beliefs/attitude (fear negative consequences of deprescribing)
Voigt, 2016	Not clearly articulated in article – content analysis	Inertia – prescriber beliefs/attitudes (no alternatives to medication/s; prescribing is kind and meets needs; stopping is difficult, futile, has/will fail – especially in relation to sedatives; Feasibility – patient (poor acceptance of alternatives); resources (time; limited availability of effective alternatives/access to specialist services) Self-efficacy – guidelines (lack of applicability to 'real-world'); information/influencers (incomplete clinical picture – framed as poor communication with other prescribers/specialists)
Anderson, 2017	Working through uncertainty: Weighing unmeasurable harms & benefits Strategies/circumstances that mitigate uncertainty Risk as a frame of reference: Deprescribing as a risk to be avoided Deprescribing as a risk to be reconciled Risk tipping points	Patient heterogeneity and complexity (Self-efficacy)- information (incomplete clinical picture; lack of evidence) Feasibility – resources constraints Feasibility – patient and/or carer (attitude to change; therapeutic relationship); inter-professional relationships and communication Inertia – prescriber beliefs/attitudes – fear unknown/negative consequences of deprescribing Work practices – proactive strategies to facilitate deprescribing **Feasibility – context (trigger to deprescribe/low hanging fruit);** Self-efficacy – confidence and experience
McNamara, 2017	Incorporation of shared decision making and patient preferences Evidence base	Feasibility – work practices (failure to elicit patient preferences/patient-centred goals); resources (time, especially for GPs); patient (physical impairments limiting communication). Self-efficacy – Information/evidence (limitation of guidelines); Influencers (junior doctors reliant on advice of senior doctors)

	Patient prognosis (focus on uncertainty) Clinical feasibility of treatment plans Optimising therapies and health management plans (lack of routine engagement) (Poor) coordination of care (very broad theme)	Self-efficacy – Information (incomplete clinical picture); Inertia – fear of negative consequences of deprescribing (also litigation for withholding preventive therapies). Feasibility – patient (framed as inability to assess patients' capacity to cope with changing treatment plans) Inertia – prescriber belief/attitude (stopping is a lower priority issue; fear of negative consequences of change); Feasibility – patient (reluctance to change); medical culture (respect other prescriber's right to autonomy & hierarchy); work practices (lack of systematic approach to deprescribing); Self-efficacy – skill/knowledge gaps (esp. junior doctors; Information/influencers (limitations of decision support tools). Inertia – prescriber behaviour – devolve responsibility to others (due to lack of key care coordinator or infeasibility of GP to take on more). **Feasibility – resources (adequate remuneration; team based approach to care, incl. nomination of key care coordinators)** **Self-efficacy – information/decision support (better evidence/guidelines; improved IT platforms**

[a] Only those themes pertaining to prescribers' barriers and enablers were extracted and included. [b] Subthemes underlined indicate findings previously not reported in the systematic review. [c] Bolded text (excluding headings) refers exclusively to enablers to minimising PIMs.

4.5 Conclusion

The thematic synthesis of studies from the original systematic review and those subsequently published indicate that prescribers' barriers and enablers to minimising PIMs, chronically prescribed in adults relate to four analytic themes: problem awareness; inertia secondary to lower perceived value proposition for ceasing versus continuing PIMs; self-efficacy in regard to personal ability to alter prescribing; and feasibility of altering prescribing in routine care environments given external constraints. The first three themes are intrinsic to the prescriber (e.g. beliefs, attitudes, knowledge, skills, behaviour) and the fourth is extrinsic (e.g. patient, work setting, health system and cultural factors).

The factors shaping prescribers' behaviour towards continuing or discontinuing PIMs are complex and highly context dependent, i.e. they are contingent on the PIMs examined, patient group and care setting. Therefore, whilst the review's findings provided a mechanism to understand and conceptualise prescribers' barriers and enablers to minimising PIMs in the international context, investigation at a local level was required to inform the development of a deprescribing intervention meeting the needs of Australian GPs caring for older people living in the community. The views of CPs would also be sought as they too had been identified as potential change agents in the Australian context. The findings of this investigation are reported in the next chapter, as is an explanation of how and which findings from Phase 1 and 2 investigations were used to inform the elements of the multifaceted deprescribing intervention to be piloted in the Phase 3 exploratory study.

Chapter 5 Phase 2 Focus group discussions with clinicians

Chapter 5 details the methods, findings and discussion of the Phase 2 qualitative investigation. The primary aims of this investigation were to explore the views of general practitioners (GPs) and consultant pharmacists (CPs) about potentially inappropriate polypharmacy, to ascertain the reasoning they apply to deprescribing in primary care, and to identify factors that support or inhibit their reasoning. The purpose of the focus group discussions in the context of the overall study design were: 1) to develop a theoretical understanding of the anticipated process of change (or barriers to it) in the local context, corresponding to the second developmental phase of the UK MRC framework for complex interventions (124); and 2) to inform the development of the elements of the deprescribing intervention most likely to support local GPs and CPs in undertaking deprescribing with their patients.

The contents of this chapter have already been published as a standalone article in *Qualitative Health Research* January 2017. The link to the full manuscript, entitled 'Negotiating "Unmeasurable harm and benefit": Perspectives of general practitioners and consultant pharmacists on deprescribing in the primary care setting', is available online at http://journals.sagepub.com/doi/full/10.1177/1049732316687732 .

5.1 Methods

5.1.1 Design and setting

A qualitative descriptive design was employed, (142) incorporating the focus group method with a sample of GPs and CPs recruited from South East Queensland (SEQ). Qualitative description is an appropriate choice in health services research based on mixed methods where a key purpose is to ascertain professionals' views on a particular topic. (142)

The rationale for using focus groups was to use a time efficient method which could also provoke detailed and valid responses not otherwise elicited during semi-structured interviews. (193) It was anticipated that group dynamics would facilitate exploration of areas of consensus and discrepancy. (194) However, in recognition of the potential for discomfort and a lack of familiarity between GPs and CPs who had not previously worked together, separate focus groups were organised for each profession. (193)

5.1.2 Sampling and Recruitment

A mix of convenience and snowball sampling was used to recruit GPs and CPs within metropolitan SEQ. A local Primary Health Network (i.e. a primary health organisation) and

founding principal of a longstanding teaching group practice assisted in identifying general practices staffed with seven or more GPs in which one GP, typically with a predisposition to supporting quality improvement activities, could act as a study sponsor. The sponsor's role was to provide all GPs within the practice written information and an invitation to participate in the research study. Existing groups of GPs in larger practices were targeted to optimise participant familiarity and comfort sharing thoughts, feelings and experiences and for recruitment efficiency. (195) GPs had to be working in primary health care with experience caring for people 65 years and older with polypharmacy who were still residing in the community. GPs who primarily serviced RACFs were excluded, recognising their responses may be influenced by the different care setting.

Potential CP participants were identified through a nationally available register of CPs and contacts of the research team. The main criterion for recruitment of CPs was experience conducting comprehensive medication reviews (CMR) through the HMR program in SEQ (by default CPs conducting CMRs will primarily see older people with polypharmacy). Individuals were approached in the first instance via email and/or phone contact and invited to participate.

5.1.3 Participants

Approximately half of all individuals invited to participate in the study agreed, such that a total of 32 GPs from five practices, and 15 CPs, participated in five and two focus groups, respectively. GPs and CPs were comparably aged, with a mean of 47 years for GPs (range 28-70, noting one participant declined to provide this response) and 48 years for CPs (range 28-63). Far more CPs than GPs were female (87% vs 44%), reflecting the nature of the CP workforce in Australia. The GPs had twice the experience, averaging 18 years in the role (range 1-50 years, with the upper limit an estimate) compared to CPs who averaged 9 years in the role (range 1-18) but again this was expected as remuneration for CMRs has only existed in Australia since 2001. Sixty-three percent of the GP participants worked full-time. Administrative rules preclude full-time equivalent hours for CPs to contain CMR program expenditure.

5.1.4 Data collection

Focus groups were conducted over a two-month period from October 2014 to December 2014. Five GP focus groups were conducted in the GPs' workplace and two CP focus groups were conducted at the University of Queensland. Each focus group was facilitated with the support of a researcher who acted as a co-facilitator. The PhD candidate, with the

support of the co-facilitator led four of the five GP focus group discussions, excluding the fifth practice where she was employed on a part-time basis and where her role was assumed by two other researchers experienced in the focus group method.

A focus group guide incorporating key topics was used to ensure consistency of approach across focus groups. In addition, the same case study of a community living older person with multimorbidity and polypharmacy, but without a terminal prognosis, was used to stimulate discussion in all focus groups. The case study was developed by the consultant general physician in the research team, in consultation with two experienced GPs with backgrounds in medical education. This was done to ensure the case study was representative of a typical multimorbid older patient that an average GP would encounter, but which showcased several examples of potentially inappropriate prescribing. The case was complemented with the question guide for focus group discussions (see Appendix 6) and presentation of the CEASE framework (see Appendix 2) to stimulate and focus conversation. (91)

Focus group discussions lasted an average of 75 min (range 55-99min) and were transcribed in real-time by a qualified transcriptionist and audio recorded for subsequent accuracy checks. Relevant field notes were made by the co-facilitator to support the accuracy of interpretation.

5.1.5 Analysis

Transcripts were inductively coded and analysed thematically using the Framework method (143). The first three transcripts (which were GP transcripts) were read and, line-by-line, independently segmented and coded text, to develop a coding framework. This process was independently repeated by a research team member. The coding framework was then discussed, reviewed and refined with one advisor experienced in conducting qualitative research. This coding framework was then applied to all transcripts digitally using *NVivo Pro 11 software (QSR International Pty Ltd, Melbourne, Australia)*. The coding framework required no significant alteration when applied to all transcripts, including CP transcripts, indicating data saturation. Data were then charted into a framing matrix to highlight patterns and linkages in the data, from which major conceptual themes were developed with the assistance of the advisory team. This final step involved revisiting the literature to interrogate and make sense of patterns from the dataset by reflecting on key concepts relevant to the topic. Extracts reflect both divergent and convergent views and were labelled with a unique identifier according to the specific focus

group by profession and the participant number (e.g. GP1, P5 = the first GP group, and fifth participant).

5.2 Findings

Two major themes were derived from the analysis: 1) *Working through uncertainty*; and 2) *Perceived risk as a frame of reference*. Deprescribing was considered by all participants as one option to improve medication appropriateness, as was therapeutic substitution, dose alteration and initiation. Table 5-1 provides an overview of the major and minor themes and subthemes elicited from the analysis. In the following presentation of these themes, key factors that support or inhibit deprescribing have been highlighted. Analysis yielded themes common to both GPs and CPs. Consequently, findings have not been separated by profession, but rather have been presented collectively, with striking differences within and between professional groups highlighted as appropriate.

TABLE 5-1 OVERVIEW OF MAJOR AND MINOR THEMES AND SUBTHEMES

Major theme	**Subtheme**	**Minor subthemes**
Working through uncertainty	Weighing unmeasurable harms and benefits	Patient heterogeneity and complexity
		Incomplete information
		Lack of evidence
		Time and resource constraints (for GPs)
	Strategies/ circumstances that mitigate uncertainty	Low risk strategies
		Patient and/or carer attitude
		Patient relationship (facilitator for GPs; barrier for CPs)
		Inter-professional relationships and communication
Major theme	**Subtheme**	**Minor subthemes**
Risk as a frame of reference	Deprescribing = risk to be avoided	Fear of unknown/harm from deprescribing
	Deprescribing = risk to be reconciled	Proactive strategies to facilitate deprescribing
	Risk tipping points	Low hanging fruit
		Clear triggers of potential medicine-related harm
	Self-efficacy	Confidence & experience

5.2.1 Theme 1 – Working through uncertainty

Focus group discussions revealed the inherent uncertainties confronting clinicians when assessing an older patient with potentially inappropriate polypharmacy, and how they resolve this in practice. This was represented by the following two subthemes.

5.2.1.1 Subtheme: Weighing unmeasurable harm against benefit

From participants' perspectives, the process of making a decision in a patient with potentially inappropriate polypharmacy involved trying to estimate and weigh up the harms and benefits of therapeutic options in the face of many unknowns in this diverse and complex patient group. This subtheme was clearly articulated by one participant who alluded to strong internal reasoning during this process:

> *The problem is that you are trying to weigh up unmeasurable harm quite often against unmeasurable benefit. We are trying to do that in our minds and trying to work out - is it more likely to be doing benefit or more likely to harm. The truth is that, in many cases, I don't know. (GP5, P5)*

Discussions made clear that nothing could be taken for granted when balancing harms against benefits in these heterogeneous patients. Even for two seemingly comparable individuals, clinicians might take legitimate actions for, or against, deprescribing depending on subtle differences in patient function, prioritisation of inferred or explicit care goals and likely future clinical trajectory, all of which can change over time between and within individuals. This meant relying on any one factor such as age when making decisions could result in erroneous decisions:

> *It depends on what she is like at 81, too. If she is really frail, you think her life expectancy probably isn't another 10 years, then I feel more comfortable stopping the statin. If she was a really good 80-year-old, who you thought – which she doesn't really sound like it from her past history – I might be more inclined to continue with the statin if she didn't have so many comorbidities. (GP3, P1)*

According to participants, a key reason for uncertainty when balancing benefits and harms of therapy was inadequate research in older polymedicated people, frequently compounded by information gaps relating to the care of individual patients. The original indication for a medicine was often unclear, due to the initiating prescriber failing to document or communicate this to other providers, as occurs typically when the patient is returned to the GP's care following hospital admission. As one participant described:

> *Sometimes, as (another participant) was saying, they come back from the hospital and they are on PPI (proton pump inhibitor) or whatever and they might have thought this is really useful because they're having some mild gastritis symptoms and then I'd normally take it off but when they come back you really don't know why*

it was started. Did they have haematemesis, you know, or was there an ulcer or something like that or was the plan for it just to be temporary? (GP1, P5)

The paucity of scientific evidence not only pertained to the concurrent use of multiple medicines but also single, commonly prescribed classes of drugs in this patient group. The lack of scientific evidence presented difficulties for professional accountability. One CP participant suggested that formulating a professional recommendation when there is uncertainty could lead to inaction:

I find statins very hard sometimes to recommend either reducing or withdrawing because there is not a whole lot of hard evidence out there as to end points, particularly when you get into this age group. Sometimes it has just been too hard to write the report so I have left it out (group laughs) … When my gut feeling is they don't need it anymore, but it's just a bit awkward. Particularly, if the patient really doesn't mind taking it and there are no other adverse effects, it stays. (CP 1, P6)

This example, as others, demonstrates an internal logic or intuitive knowledge at work (e.g. 'gut feeling'). This was reinforced by the comment from another participant, a GP, about 'keeping it in your head' when reconciling divergent opinions among specialists about the evidence of benefit versus harm. The need for readily accessible and reliable information sources as a form of security to help undertake complex reasoning in a pressured environment was emphasised in this excerpt:

Then you go to a meeting and the two specialists who are there argue completely in opposite directions. They interpret the data from this trial differently from the data from that trial. Putting that together is quite difficult. Keeping it in your head in a complex environment and limited timeframe is, I think, really the big challenge. I think, therefore, sometimes you are doing it without the really significant evidence based security - or at least I don't even know. I use UpToDate in a consult and I Google in a consult but there is only so much time you have got to be trawling through the evidence base and looking for complexity. (GP4, P4)

Participants in the GP focus groups viewed deprescribing as a time and resource intensive process, requiring not just an upfront, but ongoing commitment of effort, particularly when there are competing clinical priorities, as is often the case for the patient group in question:

So you're really setting them up for another consultation, another couple of consultations to do it properly I suppose – you can't do it at that time, you've got other priorities at the time. (GP3, P3)

5.2.1.2 Subtheme: Strategies and circumstances that mitigate uncertainty

Participants used a range of strategies, or identified circumstances, that mitigated the perceived uncertainty surrounding deprescribing decisions. Strategies included targeting medicines which are easier and less harmful to deprescribe in the first instance, adopting a gradual approach to changing medicine regimens, and deferring to patients in making a deprescribing decision. Medicines for which decisions to discontinue were endowed with greater certainty were those perceived to be overused, whose cessation was unlikely to be resisted by patients, or where a favourable outcome of withdrawal seemed more predictable. Examples of these 'easy options' included statins for primary cardiovascular prevention, bisphosphonates, proton pump inhibitors and complementary medicines. Two participants described their inclination to immediately consider these 'easier' options as:

Priority. Pick all the low hanging fruit first. (GP2, P7)

Straightaway my first thought was what are the low flying ones that we can get rid of. (CP1, P1)

However, participants acknowledged that this prioritising of the 'low hanging fruit' may deliver early wins but not necessarily the best benefit as it sidestepped drugs with potential to do more harm, such as anticoagulant and psychotropic agents and opioid analgesics.

Adopting a gradual approach with close patient follow-up was another strategy. Even for medicines that pharmacologically do not require tapering, a gradual approach served to reassure not only the patient, but also the clinician. For some GPs though, the need for prolonged follow-up which may not be remunerated, constrained their ability to promptly detect and reverse adverse effects after reducing or ceasing medications, and this constituted a barrier perceived as too great to contemplate changes. Some considered deprescribing in the hospital setting a better option:

Put them in hospital and stop everything. (GP3, P4)

The inability to maintain any follow-up with patients over time to support a gradual process of deprescribing was a major frustration for CPs. One participant cited administrative rules as an impediment to follow-up:

I think that the two-year window [for reimbursement] makes it difficult to follow-up, especially for the complex patients that need that stepwise approach. (CP2, P5)

These comments highlighted an important difference between GPs and CPs. GPs felt they lacked the dedicated time to proactively deprescribe in routine practice but suggested annual health assessments could provide an opportunity for this. In contrast, CPs, for whom comprehensive medication review is core business, had more time but lacked detailed knowledge of their patients. CPs resolved this uncertainty by adopting a strategy of posing questions to GPs about medication appropriateness, rather than making recommendations to the GP to cease PIMs.

Reinforcing a predisposition to low risk strategies, participants perceived the patient's attitude towards deprescribing as a factor in balancing benefit against harm. Further, as one GP participant reported, a patient's attitudes to change could relieve the clinician of any responsibility for deprescribing:

Even if you don't know what right and wrong is, you don't necessarily have to provide the answer. It will be the patient that will provide the answer as to how willing they are to stop something… (GP5, P6)

An underpinning element to *working through uncertainty* in regard to deprescribing was the consideration of relationships. For GP participants, a continuous therapeutic relationship with a patient was critical to better assessing harms and benefits and committing to the potentially protracted process of deprescribing:

But that's the starting point - to establish what the relationship is. I guess that's my point. So, until you know what the relationship is - whether it is an on-going relationship or whether it's an episodic one; then that would lead to where you take the consultation and if it's appropriate. That's the starting point: who the person's primary GP is. (GP2, P5)

Under-developed inter-professional relationships (e.g. between GPs and CPs or GPs and specialists) was seen as hampering the deprescribing process, largely due to poor communication and insight into each other's decision making. Good working relationships, i.e. between GPs and CPs or in the following case between a GP and specialist, facilitated timely, collaborative deprescribing decisions:

That strategy of phoning specialists there and then, in front of them - we collaborate on this and this is what we are doing. (GP5, P6)

Unsurprisingly, specialists were deemed highly influential in shaping not only clinicians' but also patients' willingness to consider deprescribing due to their perceived higher authority.

I do think one of our biggest barriers is our specialist colleagues because [patient comment], "Doctor X said I must never, ever stop that." (GP5, P2)

Better evidence that deprescribing is safe and effective and decision support provided in a format that is easily accessible at the point of care (e.g. integrated into the practice software) for use in discussion with patients, was offered by participants as a key facilitative strategy. However, in regards to decision support, when participants were asked about the utility of the CEASE framework (the published decision framework to support deprescribing) (91), the clear consensus was that it would not be used at the point of care by experienced clinicians who already had internalised its individual steps into their prescribing reasoning.

I think in practice you are not going to use it, myself. I think we have already intellectualised it. (GP5, P2)

I think that is a very intuitive thing, anyway. (CP1, P6)

The value of the CEASE decision framework, if any, was as a tool for education and reflection, especially for junior clinicians.

I think it would be very good for people starting out in general practice to have that so they can approach it logically. (GP5, P4)

This theme shows that clinicians have to contend with considerable uncertainty when faced with the dilemma of problematic polypharmacy in this diverse and complex patient group. Various strategies are used to mitigate uncertainty, and are influenced by many contextual factors. As the next major theme indicates, a decision to intervene is influenced strongly by how clinicians conceptualize the risk attached to polypharmacy and deprescribing.

5.2.2 Theme 2 – Perceived risk as a frame of reference

As can be inferred from comments in *working through uncertainty*, perceived risk was shaping participants' views about deprescribing. However, *perceived risk as a frame of reference* warrants its own discussion as a second major theme since it denotes

something much deeper than strategies and processes intended to resolve uncertainty, and offers a window into participants' internal reasoning. There were differences among participants in their risk framework but also some consensus in relation to the tipping points in risk perception which might facilitate deprescribing. These findings are discussed in the following two subthemes.

5.2.2.1 Subtheme: Deprescribing as a risk to be avoided or reconciled

Participants demonstrated varying perspectives on the level of perceived risk surrounding deprescribing decisions. However, two contrasting risk frames of reference were distinguishable in the comments as discussed below.

5.2.2.1.1 Risk to be avoided

Contributing to the risk to be avoided frame was the unpredictability of the outcome trajectory of deprescribing, which is unsurprising given the issues discussed in the first theme. However, this unpredictability introduced fear of the unknown and fear of harm, which was used to justify not taking any action:

> *The thing is, it is not often easy to tell if something is having no effect on persistent symptoms. They might be a whole lot worse if you stop it. That's the thing that you don't know. (CP2, P6)*

> *Fear, that they'll have a negative outcome from you reducing some of these medicines. (GP2, P4)*

Likewise, the fear of contributing to a worse outcome, possibly death, as a result of deprescribing was part of the justification for maintaining the status quo. As this participant revealed, the more unstable or ill the patient or the more complicated the issues, the better to find an alternative path to avoid creating a more serious risk, especially among patients who express no desire or expectation for change in their medicines:

> *Sometimes people just come in and say, "I want my scripts", and they don't really care if you don't do anything more than measure their blood pressure. You have got a professional duty of care and …if you have got a sorry history, you don't really want to contribute to another event. It can be a terminal event; it can become a risk. It becomes serious. It means that you wouldn't also stop some medicine that protects their bones, alendronate, cholecalciferol, Caltrate. Even (if) the Caltrate is contributing to the constipation, find something else to blame. (GP5, P6)*

In both cases, risk perception was in one direction – the risk of harm incurred by deprescribing irrespective of the risk of harm incurred by continuing potentially inappropriate polypharmacy.

5.2.2.1.2 Risk to be reconciled

The contrasting frame of reference was to perceive deprescribing as a proactive attempt to reconcile risks of maintaining the status quo versus risks of deprescribing. For some GP and CP participants, the continuation of problematic polypharmacy incurred a risk of future medicine-related adverse events which should not be dismissed. Taking this frame of reference, one participant preferred to view polypharmacy as an emergent health problem that warranted proactive intervention like any other such as stroke or heart attack, particularly with advancing age:

> *I think one solution to it is to actually indicate that polypharmacy is a problem (to the patient). "It's a health problem. So, risk of stroke is a problem, there are all these other problems but this is another one. And this one's becoming more dangerous as you're getting older." That risk is up there with the other risks and why you want to do something. (GP2, P7)*

One of the CP participants went further by inferring that disclosing a risk of medicine-related harm in a considered and polite way, and making a recommendation to discontinue, was a professional obligation, even if the GP or others may not accept it. This sentiment met with group approval:

> *If it is something serious, I think we still do - we spend a lot of time rewording so that it doesn't sound like we are being bombastic in our approach, that we you know, we just want the doctor to consider it and to think about it and he may not take it on board initially, but I think you still have to put it down. …you can't not put it down because that could be dangerous too, especially if down the track you have somebody come back and say, "Why didn't you pick that up?" (CP1, P7)*

Interestingly, the undertone of fear expressed relates to fear of not being seen to intervene, as opposed to the fear of intervening.

The participants who perceived deprescribing as involving risks to be confronted also expressed a desire to proactively identify deprescribing opportunities and discuss these with their patients. However, as expressed here, part of the challenge was addressing and

recalibrating the risk perceptions of patients, some of which may have a long history and were influenced by past encounters with specialists:

> *…Sometimes they say to me, "The specialist told me I've got to stay on this for the rest of my life". You go, "Well, in this setting 20 years ago, that was the recommendation but the evidence basis has changed so maybe that might be something you can reconsider", so that might have a shift, get them to start thinking that maybe that whatever someone told them 20 years ago may be something that you could, that needs to be done differently. (CP2, P6)*

5.2.2.2 Subtheme: The risk tipping points

Arguably, those with a risk to be avoided frame of reference needed more convincing evidence or overt indications to deprescribe, whereas those with a risk to be reconciled frame of reference demonstrated a willingness to consider competing risks and deprescribe when the benefit/risk equation was in its favour. Scenarios which favoured the latter and which attracted consensus among participants comprised overt adverse events or specific situations such as falls, patient non-adherence, and direct requests by patients/carers to cease medicines:

> *If it is very obvious like an adverse effect, I feel more confident… I think, if it is somebody who I know, I know their background, what the plan is and where we are heading, I am involved in the care relationship with them, that gives me confidence. (Other participant)'s patient coming to me because they need another script, then I don't worry about it and I'm not so confident. (GP1, P6)*

What is also notable in this extract is that, as an external trigger, an adverse event could engender more certainty and confidence in some participants to act, although not universally:

> *That is a clear trigger to make a decision, the fact that previously he hadn't been falling; he was getting more benefit than risk. And then, he starts having some stage, he falls, so the risks start to outweigh the benefits and it's easy to have the discussion, "Now that you are falling over, this medication is more risky so therefore we are going to stop it". You can do that with complete confidence. (GP4, P2)*
>
> *Semi-complete confidence. (P4)*
>
> *Yeah. (Group agrees)*

These comments indicate that the risks entailed in decision-making are rarely unidimensional as other factors, such as the therapeutic relationship noted in the first theme, are taken into account. This explains, in part, the variability in how participants might view risks and respond. These extracts also highlight the extent to which confidence dealing with uncertainty is required for self-efficacy in deprescribing. It is likely that those with a risk to be reconciled mindset make their own judgements about ceasing medicines rather than justify the status quo by deferring to past expert opinion, as expressed in the following extract:

> *I think, if you are not comfortable in your own skin, in your abilities as a clinician, it is much easier to pay attention or to go along with what the 'expert' says. Therefore, you end up building up a list of medicines. It might be 10 years from the last time that person was seen by that specialist but still it becomes part of their DNA, so to speak. (GP1, P7)*

This was reinforced by an example provided by one CP participant who perceived that a lack of confidence in clinical ability had deterred a GP from taking action where a specialist was involved:

> *I was doing this HMR and this patient had a few issues and he (the GP) said he (the patient) was being looked after by the specialist, (so) don't worry about it. Even if I made any suggestions… I think it is the confidence of the doctor (the GP). (CP2, P1)*

Experience might also contribute to self-confidence and how risk is viewed. Negative experiences reinforced a tendency to opt for the status quo, whereas positive or neutral experiences fostered open mindedness towards deprescribing. In the following interaction regarding statins for stroke risk reduction, the absence of a negative consequence from ceasing a statin served as a reminder to one GP participant that the fear of adverse withdrawal effects might be overstated. The exchange between these participants demonstrates how repeated positive experiences can shift the risk frame. It also again reinforces the desire for better evidence that deprescribing is safe and effective:

> *I think there is that fear we will stop it and have a stroke the next week but I think that fear might be a little bit – (GP5, P4)*
>
> *Exaggerated. (P6)*

Exactly. (P4)

It would be good to have some figures so - there is going to be a big push to be not prescribing statins forever - so some figures to back it up. (P3)

I think, as you get older, you realise that is not really true because you have done it so many times and they have not had a stroke the next week. (P4)

Experience comes into it. (P2)

As this theme indicates, the way clinicians frame issues and risks inherent to polypharmacy significantly affects how clinicians decide whether to persist with the status quo or deprescribe. There are clear triggers which can tip the balance toward deprescribing for both professional groups but self-efficacy and prior experience with discontinuing medicines also play a part.

5.3 Discussion

These findings indicate deprescribing is an inherently uncertain venture for both GPs and CPs and the internal reasoning underpinning decisions is complex. The option to deprescribe is shaped by many factors, including a clinician's perception of the risk/benefit ratio of persisting with the status quo versus deprescribing. As summarised in Figure 5-1, deprescribing is more likely to occur in the presence of a continuous therapeutic relationship between the GP and patient and in response to a clear clinical trigger or the finding of 'low hanging fruit'. On the other hand, poorly developed inter-professional relationships and a lack of dedicated time and tacit knowledge/familiarity with patients for GPs and CPs are important barriers to deprescribing.

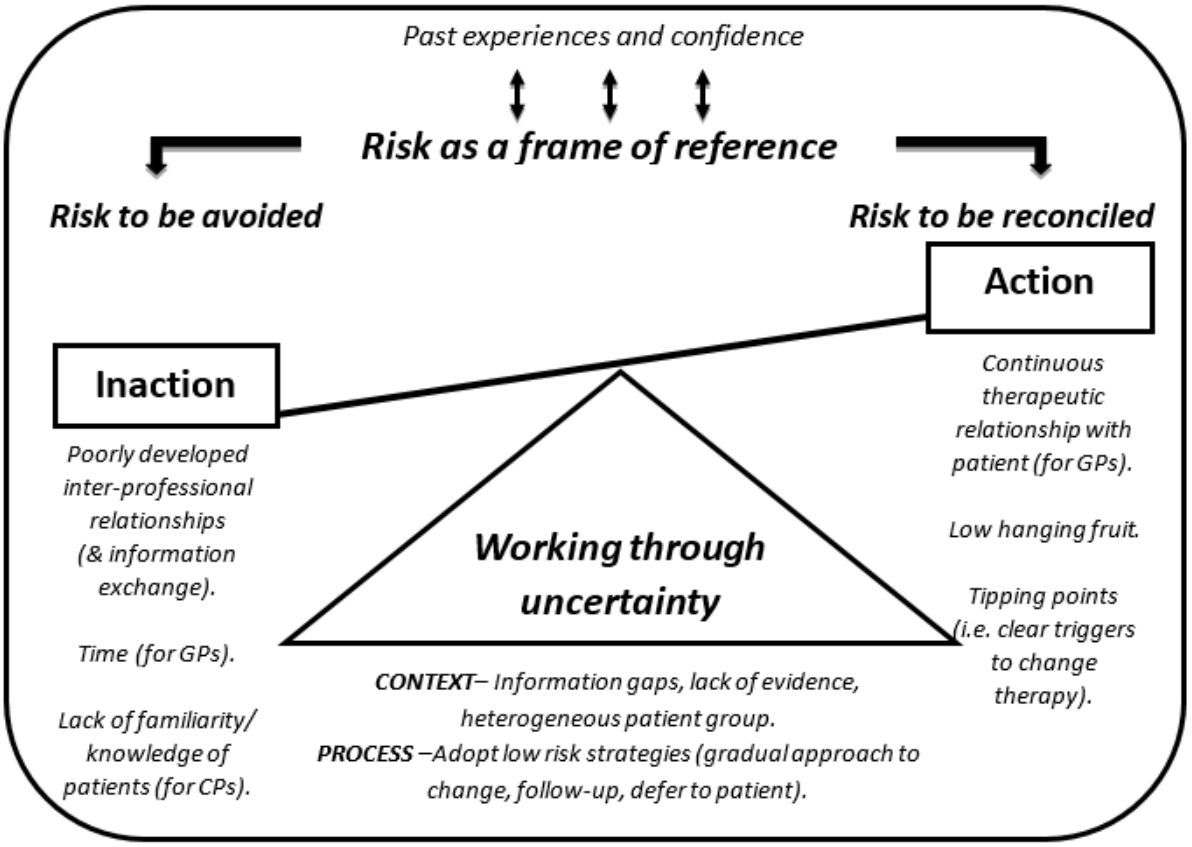


FIGURE 5-1 RELATIONSHIPS BETWEEN THEMES AND CRITICAL CONTINGENCIES FOR DEPRESCRIBING

Note. GPs = general practitioners; CPs = consultant pharmacists

This in-depth analysis of how and why both GPs and CPs in clinical practice consider deprescribing decisions in community-based older people with polypharmacy adds to the literature on prescribers' barriers and enablers to reducing potentially inappropriate polypharmacy (154-157, 196, 197). Similar to previous research on how clinicians decide if initiating new medicines is likely to confer more benefit than harm (198), when contemplating deprescribing, clinicians sought to determine the balance of probability of harm versus benefit in deciding whether to persist with the status quo or deprescribe. There are however some unique differences between initiating therapy and deprescribing. Not knowing the original indications for existing medicines and a lack of scientific evidence for deprescribing instil more uncertainty into decision-making. Moreover, the act of prescribing a medicine is often in response to a problem that the patient presents to the clinician. The challenge with deprescribing, however, is that the patient with polypharmacy

often does not present with a recognisable clinical syndrome and, even those who do manifest clinical features of medicine-related harm, are often labelled as suffering unrelated geriatric syndromes or simply the effects of ageing or chronic ill-health (3). This may help to explain the finding that approaches to deprescribing appear largely reactive i.e. clinicians require a clear clinical or situational trigger such as a patent adverse event or near and obvious risk of harm (clear and present danger) to cease a medication.

This analysis indicates that the way clinicians work through uncertainty and their predisposition to deprescribe appears strongly influenced by their framing of risk in regard to continuing or ceasing medication. Commission or regret bias arising from ill-fated action may partly explain a clinician's hesitancy to proactively manage potentially inappropriate polypharmacy (198). For participants in this study, continuing with the status quo might provide the yard stick against which the consequences of any alternative course of action is compared, and losses resulting from alternative actions tend to loom larger than gains (199). The seriousness of negative deprescribing consequences in clinical practice compounds this issue. For example, the consequence of an embolic stroke in an older person with atrial fibrillation in whom an anticoagulant is ceased because of high bleeding risk is tangible. On the other hand, the avoidance of a major intracranial bleed by ceasing the anticoagulant is not, potentially skewing the weighing of harm/benefit and framing of risk in the clinician's (and patient's) mind.

These findings echo those of Sinnott *et al* in that GPs use a range of decision making strategies to reconcile therapeutic uncertainty in multimorbid patients (196). Their major finding was the use of 'satisficing' by GPs (pursuing an acceptable, rather than 'ideal' therapeutic regimen). Whilst this term was not used in the current study, both GPs and CPs did individualise therapy according to a patient's unique circumstances. Common to both analyses was the use of 'gut feelings' by clinicians and deferring to patients or specialists in resolving uncertainty, although Sinnott *et al* highlighted the largely facilitative role of the specialist. These findings uniquely suggest that clinicians' conceptualisation of the risks attached to different prescribing options profoundly influence whether they make or do not make changes. The fact that, in this study, GPs were specifically questioned regarding minimisation of problematic polypharmacy, whereas Sinnott *et al* took a broader view of management decisions in multimorbid older people, may explain the difference in findings. Apparent from both analyses is that, when dealing with prescribing decisions in

complex patients, neither the process for arriving at a decision (for each clinician) nor the clinical course and outcomes (for a patient) is linear or predictable.

In the earlier systematic review of prescribers' barriers and enablers to minimising PIMs in adults (9), four major themes were identified: problem awareness; perceived value for ceasing versus continuing PIMs; self-efficacy in regard to personal ability to alter prescribing; and feasibility of altering prescribing in routine care environments given external constraints. The findings of the focus groups complement those of the systematic review. Participants' mention of medications commonly cited as being overused in the medical literature as 'low-hanging fruit', reinforced how greater awareness primes clinicians to consider certain medicines for deprescribing. Moreover, in the absence of 'low hanging fruit' or a clear trigger to cease therapy, deprescribing, compared with initiating therapy, appears a riskier, less certain, and more cognitively and socially demanding process, with minimal decision support. This helps to explain the predisposition towards therapeutic inertia in the absence of a 'risk to be reconciled' frame of reference and high self-efficacy. This study also reinforces the complex interactions between contextual factors which affect the feasibility of deprescribing.

5.3.1 Strengths and Limitations

In addition to the use of rigorous and reproducible methods for data collection and thematic analysis, this study provides unique insights into the reasoning GPs and CPs apply to deprescribing and how this is shaped by their perceptions of risk. Understanding this process is a critical first step to assisting clinicians in partnering with patients to improve quality use of medicines through deprescribing.

Given that participants were a convenience sample confined to GPs and CPs in one geographic region in Australia, this may limit the generalisability of findings. Similarly, the case study focussed on older adults residing in the community so these results may not be generalisable to deprescribing decisions involving institutionalised populations with morbidity that is more advanced and prognoses that are more predictable. Furthermore, other prescribers of medicines, such as medical specialists, were not included although they clearly exert a strong influence on prescribing decisions.

Efforts were made to limit the impact of any prior professional relationship between focus group facilitators and participants on their responses, although it is impossible to rule out a

social bias effect from this. Techniques such as revisiting and challenging potentially socially desirable responses were used to ensure the validity of findings.

5.4 Conclusion

The findings in this chapter indicate that deprescribing requires an estimation and comparison of benefits and harms of ceasing medicines which are inherently uncertain in this complex and heterogeneous older patient group. GPs and CPs use a range of strategies to mitigate this uncertainty which is heavily influenced by the clinical context and the way the GP or CP frames deprescribing risk. The learnings from these focus group discussions, informed by the principles of behaviour change interventions described in Chapter 2 and findings of the Phase 1 systematic review were used to inform the development of the elements of the multifaceted intervention. The intervention and full methods of the Phase 3 exploratory study are described in the next chapter.

Chapter 6 Phase 3 Exploratory mixed methods study methods

Chapter 6 describes the methods for Phase 3 which is the mixed methods exploratory study. As described previously, this phase represents early-phase piloting and developmental work, informed by the UK MRC guidance for complex interventions. This chapter details the study: aim and objectives; design and setting; process for sampling and recruitment; intervention; outcome measures; and procedure for data collection and analysis.

Given the pragmatics of scope and time for a PhD, this exploratory phase was time-limited, with only four-months elapsing between commencement of the intervention and follow-up data collection. Consequently, although Phase 3 aims to answer whether a GP-led deprescribing intervention *can* be done, and done safely in the short-term, it does not address other important issues, such as the long-term safety and effectiveness of the intervention and whether the intervention can be implemented and sustained on a wider-scale. Subsequent studies, including a larger cluster RCT evaluating patient outcomes over the longer term, would be required to address these questions, which is beyond the scope of this PhD study.

6.1 Study aim and objectives

The aim of the mixed methods exploratory study was to pilot and evaluate the feasibility, effectiveness and safety of a multifaceted GP-led intervention in community living older people in primary care, developed from Phases 1 and 2.

Study objectives pertaining to effectiveness (reported in Chapter 7) included:

- To investigate the impact of a multifaceted deprescribing intervention on the medication regimens of older community based patients with polypharmacy
- To investigate the impact of a multifaceted deprescribing intervention on patient's attitude towards their medication regimen and self-reported health status

Study objectives pertaining to safety (reported in Chapter 7) included:

- To investigate reports of suspected/actual adverse events or experiences arising from the multifaceted deprescribing intervention

Study objectives pertaining to feasibility (reported in Chapter 8) included:

- To explore how the multifaceted deprescribing intervention was adopted in practice by GPs

- To explore how acceptable the deprescribing intervention was perceived by GPs and patients and how likely, if at all, the intervention could be sustained over the longer term

The mean difference in the number of agreed regular medications deprescribed per person was the primary outcome (Objective 1). A range of secondary outcomes and measures were reported to address the remaining objectives. See section 7.4, 'Effectiveness outcomes – Medication-specific outcomes', for details and definitions of the primary and secondary outcome measures.

6.2 Overview of design, setting and timing of data collection

A non-randomised, controlled pre-post mixed methods design was used. Both quantitative and qualitative data were collected and analysed to assess the feasibility and impact of the intervention in primary care. The study involved five general practices and 20 GPs in Metropolitan SEQ across two study arms: an intervention arm comprising 10 GPs working at three sites who were exposed to the intervention, and a control (herein referred to as 'usual care') arm of 10 GPs at two sites who delivered usual care. The intervention was targeted at the level of the clinician, with quantitative and qualitative measures gathered at the clinician and patient level. Quantitative data were collected from the intervention and usual care group before and after exposure to the intervention. Qualitative data were collected at follow-up from the intervention group to explain quantitative findings and explore participants' views regarding the feasibility of the intervention. (140) An overview of the study design and timing of data collection is shown in Figure 6-1.

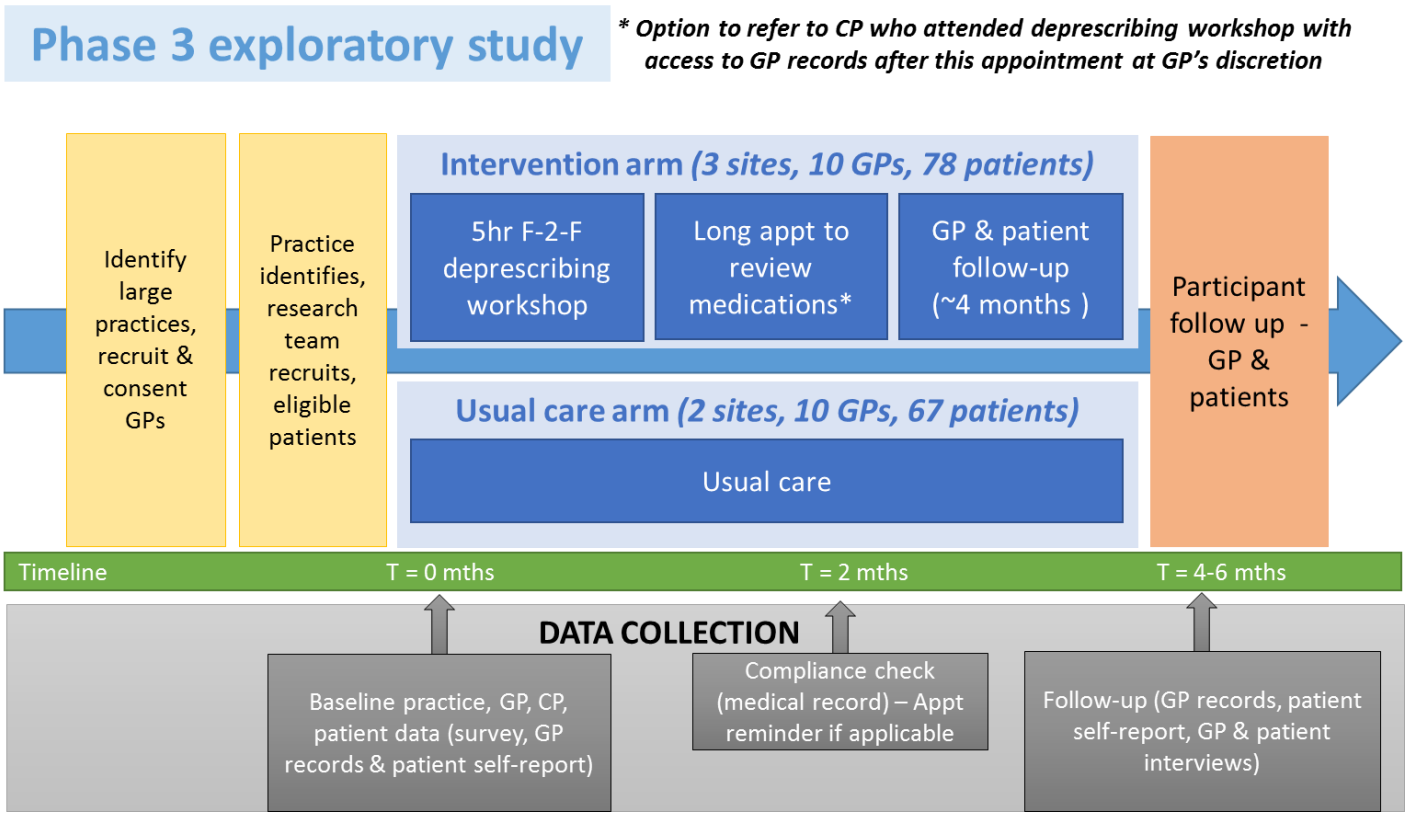


FIGURE 6-1 PHASE 3 EXPLORATORY STUDY DESIGN OVERVIEW

(F-2-F = face-to-face; appt = appointment).

6.3 Recruitment

6.3.1 Participants

Recruitment involved three participant groups: 1) general practitioners; 2) consultant pharmacists; and 3) patients.

6.3.1.1 General Practitioners (GPs)

Inclusion criteria:

- Working in primary health care and caring for community living older people with polypharmacy
- Available to attend a deprescribing training workshop in August or September 2015 (intervention arm only)
- Working the equivalent of four or more, three-hour sessions per week (to ensure adequate access for patients to their usual GP)

Exclusion criteria:

- Primarily caring for people aged 65 years or older with polypharmacy residing in aged care facilities (as this was not the care setting of interest)

While it was intended to recruit a diverse sample of GPs based on age, years of experience and gender balance, it was anticipated that GPs who had been in practice for a longer period may see a higher proportion of older patients compared to more recently qualified GPs. It was therefore accepted that the eligibility criteria may naturally lead to the recruitment of more experienced GPs and this was accepted as a limitation of the study.

6.3.1.2 Consultant Pharmacists (CPs)

Inclusion criteria:

- Experienced in and/or actively conducting Home Medicines Reviews (HMRs) (5 or more years since attaining accreditation preferred)
- Available to attend a deprescribing training workshop in August or September 2015
- Willing to travel to provide HMR services to patients of recruited intervention practices

Exclusion criteria:

- Conduct medication reviews primarily for residents in aged care facilities (as this was not the population of interest)

6.3.1.3 Patients

Inclusion criteria:

- Active patient of the practice as defined by the Royal Australian College of General Practitioner (RACGP) standards (i.e. had attended the practice three or more times in the past two years) and a regular patient of one of the GPs recruited to the study
- Aged 65 years or older and living in the community (and not in a RACF)
- Taking eight or more regular medications as listed in the GPs electronic medical records
- Capacity to give consent
- Proficient in speaking and reading English
- Contactable by telephone

These criteria were selected given the evidence of harm in patients aged 65 years and older with polypharmacy. The minimum threshold of eight regular medicines as reported in the GP's electronic record was arbitrary in identifying potentially eligible patients but selected on the basis that medication lists were likely to be out of date and inflated due to the inclusion of past prescriptions of time-limited courses of medications used to treat acute conditions which had since resolved. (200) To address this, when phoning patients identified as potentially eligible for the study, only those taking five or more prescribed medicines each day would be recruited, as five medications was the threshold above which harm has been shown to become evident. (69) The rationale for English proficiency

and the need to own a functioning telephone was that questionnaires would be administered pre- and post- intervention over the telephone by the research team.

Exclusion criteria:

- Confusion, cognitive impairment, mental health disorders with psychosis and/or communication difficulties (as documented or confirmed by the patient's GP) that would preclude informed consent
- A terminal illness (life expectancy less than six months) (201)
- A Home Medicines Review (HMR) in the 12 months prior to recruitment

These criteria were selected due to the ethical requirement to recruit patients with capacity to give informed consent. Patients with a terminal illness were excluded as it was anticipated that higher rates of deprescribing may be seen in this patient group and they were not the focus of the intervention. Patients who had had an HMR in the past 12 months were excluded given the potential for medication lists to have been recently reviewed, with inappropriate or unnecessary medicines potentially already ceased in this group by GPs likely to be motivated to consider the issue. It should be noted however that, if an HMR occurred between recruitment and data extraction, this was considered to have occurred within the study period and so was simply recorded.

To minimise the potential to cause harm and to meet the University of Queensland's ethical requirements, under exceptional circumstances, a GP could review eligible patient lists and exclude an individual who he or she felt may be distressed or harmed by contact with the research team. Examples included individuals prone to extreme anxiety if contacted by strangers or who had a history of significantly poor adherence to medicines. In these instances, the GP was required to provide the rationale for excluding a patient to mitigate potential selection bias.

6.3.2 Method of recruitment

6.3.2.1 Recruitment of GPs

A mix of convenience and snowball sampling was used to recruit GPs within metropolitan SEQ. Greater Metro South Brisbane Medicare Local (subsequently renamed Brisbane South Primary Health Network [BSPHN]) assisted in identifying practices within their catchment staffed with seven or more GPs. Larger practices were targeted as nodes for GP recruitment in the interests of efficiency and to ensure comparable practice sizes. A shortlist of practices was developed in which a contact, known to the research team or their associates, could act as a study sponsor. The role of the sponsor would be to assist

with access to the site and recruit GPs. Typically, the potential sponsor was a principal, practice manager or GP with a predisposition to supporting quality improvement activities within BSPHN.

Phone calls to the study sponsors were made outlining the study. Written information was then sent via email or fax with an invitation to participate to all GPs in the practice. The sponsor GP would then indicate, on the site's behalf, the practice's willingness to participate in the study and, if so, as either an intervention or usual care site. The PhD candidate conducted face-to-face meetings with interested practices to detail study requirements and facilitate individual GP recruitment and to obtain their written consent.

From a list of 15 practices in whom sponsors were contacted, five were recruited to participate – three intervention sites and two usual care sites. One of the usual care sites was recruited outside the BSPHN catchment due to their willingness to participate. This occurred at a time when other practices that had already been approached to participate had declined and recruitment deadlines had already been breached.

6.3.2.2 Recruitment of CPs

Recruitment of CPs occurred after recruitment of practices as one of the eligibility criteria for CPs was their willingness to travel to provide HMR services to patients of recruited intervention practices. CPs were recruited by convenience sampling, as contacts known to the research team to be actively conducting HMRs in the BSPHN area. The number of CPs to be recruited would be contingent on the number of intervention sites for whom HMR services would possibly be required. A sufficient number would be that which could ensure timely provision of HMR service should GPs in the intervention arm refer patients for HMR. Individuals were approached in the first instance via phone contact, with information provided in writing prior to obtaining written consent.

6.3.2.3 Recruitment of patients

A detailed process was developed and provided to all participating GPs and practices so that a shortlist of up to 15 to 20 patients meeting the study's eligibility criteria could be generated per GP (see 6.4.1.1, Identification of a consecutive sample of eligible older patients with polypharmacy). This would allow for patient refusals such that a minimum sample of five patients per GP could be recruited to the study. Figure 6-2 summarises the process and is explained below.

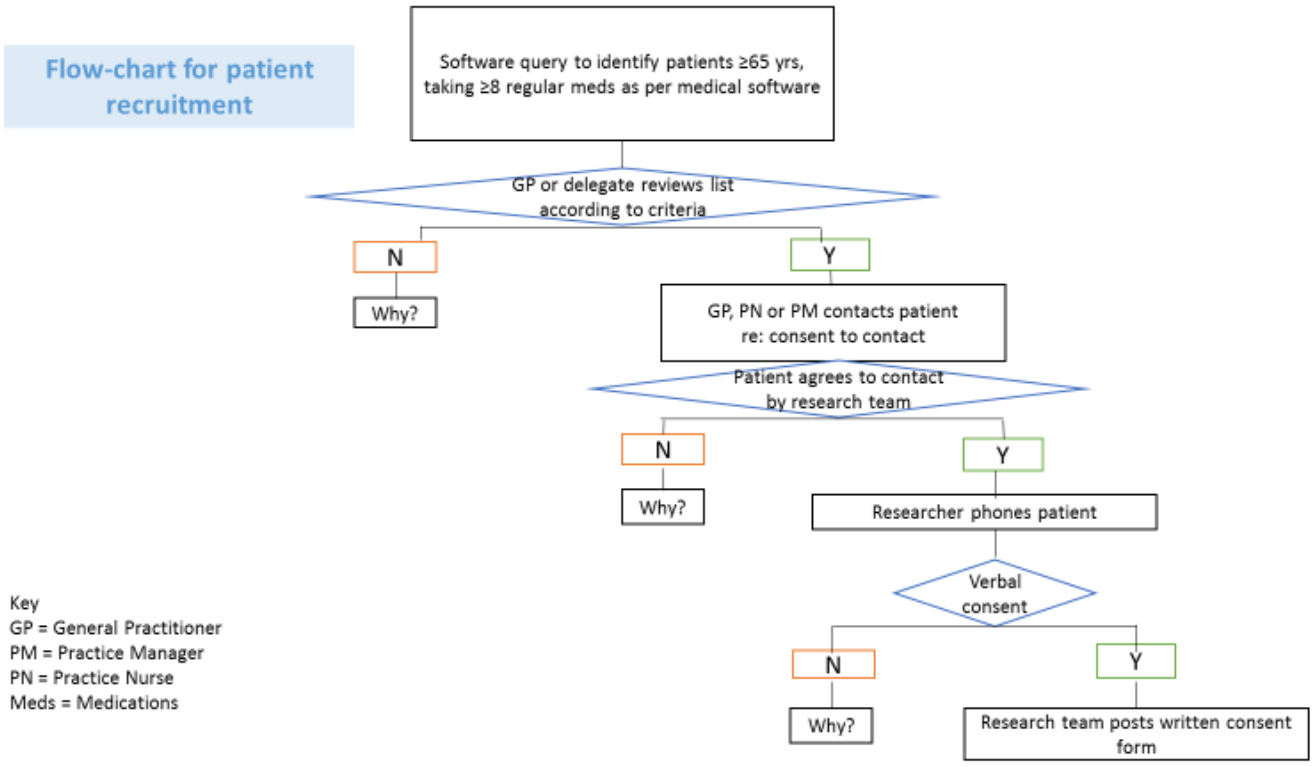


FIGURE 6-2 FLOW CHART FOR PATIENT RECRUITMENT

Once each GP had a consecutive list of 15 to 20 active patients meeting the eligibility criteria, GPs (or where appropriate, a practice nurse/manager liaising with the GP) contacted eligible patients in person or by phone to gain verbal consent to be contacted by the research team. Where 'consent to contact' was obtained, the PhD candidate contacted patients by phone with further details about the study and an information sheet and consent form were mailed to interested patients. During this initial phone call, patients were asked to confirm they were taking a minimum of five prescription medications daily. Those patients who did not fulfil these criteria were excluded from participating.

6.3.3 Sample size

Arbitrary minimum recruitment targets were set to test the feasibility of the intervention including –

- Three GPs per site (so the number of practices with whom to liaise was manageable)
- Ten GPs each in the intervention and usual care arms
- Five patients per GP

In total, a provisional sample size of 150 patients (approximately 75 each in the intervention and usual care arms of the study) was determined for this exploratory study. There was limited data available on which to base the sample size. A feasibility study in

which the CEASE deprescribing guide was applied to acute hospitalised older patients with polypharmacy (defined as eight or more regular medications in this study) in the inpatient setting demonstrated a statistically and clinically significant effect in a sample of 50 patients. (118) The primary care cohort in this study, however, would be potentially healthier and more robust, and deprescribing would be more likely to be anticipatory, rather than reactive (i.e. in response to a hospital admission), making the process of deprescribing, and its benefits, potentially more difficult to achieve. For this reason, it was speculated a larger sample would be required. It was also reasoned that the larger sample size would deliver a suitably diverse patient group with respect to age, gender, comorbidity burden, chronic prescription medication load and usual GP, whilst also allowing for patient drop-outs.

6.4 The intervention

The multifaceted, GP-led deprescribing intervention was designed based on principles of behaviour change as described in section 2.4 ‘Changing practice in primary care’ and the findings of the Phase 1 and 2 investigations. The way in which this information was used to design the complex intervention is detailed in Table 6-1.

TABLE 6-1 ELEMENTS OF THE GP-LED DEPRESCRIBING INTERVENTION, AS INFORMED BY PRINCIPLES OF BEHAVIOUR CHANGE AND PHASE 1 AND 2 FINDINGS

Principle of behaviour change(127)	**Mapped to concept from systematic review (Phase 1)**	**Focus group finding (Phase 2)**	**Element of the intervention indicated (Phase 3)**
Systems change Audit & feedback	AWARENESS	A continuous therapeutic relationship is a critical contingency for GPs to deprescribe	Work with practices to develop and implement a software query to identify eligible participants who are regular patients of GPs recruited to the study
Systems change	FEASIBILITY	GPs felt they lacked the opportunity to conduct comprehensive medication review in routine care	Work with practice staff to schedule an extended appointment for study participants with the express purpose of comprehensive medication review
Systems change Education & training	FEASIBILITY		Have experienced CPs attend the deprescribing workshop and be available to provide HMR services to patients at the intervention sites, should the GP wish to engage them.
Environmental restructuring	FEASIBILITY	CPs, for whom medication review is core business, had time, but felt they lacked adequate information/knowledge about the patients	Facilitate full CP access to medical records and/or place CP within practice/s should GPs refer patients for HMR
Education & training Role modelling	INERTIA & SELF-EFFICACY	Clinicians who perceived deprescribing as entailing risk to be reconciled, rather than avoided, reported greater inclination to consider and seek out opportunities to address potentially inappropriate polypharmacy	Develop a deprescribing workshop and key opinion leader to present evidence to raise awareness of potentially inappropriate polypharmacy to recalibrate perspectives on the potential for harm of potentially inappropriate polypharmacy, and the safety of deprescribing

Education & training	SELF-EFFICACY	A lack of scientific evidence and clinical information gaps regarding the future benefits and harms of medications were major contributors to uncertainty when deciding if medications were potentially inappropriate and hence eligible for cessation	At the deprescribing workshop, review the available evidence of benefit and harm of commonly prescribed medications in older people and identify scenarios where cessation may be appropriate
Education & training	SELF-EFFICACY	Clinicians felt that the CEASE framework[a] may be useful for reflection and learning but was not easy to apply at the point of care	Apply the CEASE framework[a] to case studies during the deprescribing workshop for learning. Where relevant, have participants identify elements of the CEASE framework directly applicable to deprescribing in clinical practice
Systems change	FEASIBILITY	Integration of decision support relating to deprescribing into GP software	Co-design (at the deprescribing workshop) an auto-fill template for use by GPs during deprescribing consultations which included prompts from the CEASE (if acceptable/desired by GPs).

[a]CEASE framework refers to: ascertaining all Current medications; assessing the level of Elevated risk of medication-related harm in an individual patient; Assessing each medicine for usefulness in relation to its potential benefits and harms; Sorting medicines – prioritising medicines for discontinuation; and Eliminating medicines according to a structured discontinuation protocol. (91)

6.4.1 Operationalising the intervention elements for practices, GPs and CPs

6.4.1.1 Identification of a consecutive sample of eligible older patients with polypharmacy

Working closely with practice principals (or delegates) of recruited GPs, a standardised but customisable patient management software query was developed and run to help identify eligible, active patients of those GPs. This involved the use of the same medical software (Best Practice® Software) at all but one site. A comparable query was performed using an external reporting software tool (Pencat®) at the site that used different software (Medical Director®).

To account for variations in data quality across the sites, the software query was combined with a documented manual screening process so that each GP (or practice delegate) could generate a sample of consecutive eligible patients for study recruitment. This procedure can be seen in Appendix 7.

6.4.1.2 Deprescribing workshop

Adult learning principles informed the development of the five-hour, face-to-face deprescribing workshop for GPs and CPs. A consultant general physician and expert in deprescribing delivered a one-hour didactic summary of the evidence for deprescribing, with the aim of reframing the benefits and harms of polypharmacy and deprescribing. The rest of the workshop was interactive. Three hours were spent working through two cases – one fictional and one real (supplied in advance by one of the attending GPs) – in which the CEASE framework was applied systematically to each case in identifying PIMs eligible for deprescribing.(91) Facilitated group discussions followed, including evidence summaries for the PIMs to be deprescribed, barriers and facilitators anticipated in practice, and resources available to support deprescribing. The final hour of the workshop involved group interaction with, and feedback on, the autofill template for use by the GPs during deprescribing appointments. GPs were asked to import the template into the consultation notes section of the software during deprescribing appointments. The template served three purposes: 1) a data collection tool; 2) decision support, prompting GPs to consider and apply key steps in the CEASE protocol during a deprescribing appointment; and 3) a framework for the GP for documenting the deprescribing consultation. See Appendix 8 for the auto-fill deprescribing template. Each participant was also provided with a deprescribing resource kit which provided a summary of available resources for further reading/decision support.

6.4.1.3 Deprescribing appointment between GPs and patients

Practice administration staff were responsible for ensuring that each intervention patient had an extended appointment (known as a deprescribing appointment) scheduled with their GP after that GP had attended the deprescribing training workshop. In the booking process, reception staff reinforced with patients the need to bring all medicines (prescribed, over the counter [OTC] or complementary) to this appointment. Approximately two months after the training workshop, practice staff were prompted to schedule any outstanding initial deprescribing appointments with recruited patients. At this time, a follow-up email was sent to GPs encouraging them to see any patients who were yet to have their initial deprescribing appointment. In this email, GPs were provided with the protocol for alerting the research team to any actual or suspected deprescribing adverse effects (see Appendix 3 for a copy of this form).

6.4.1.4 Referral to CPs for HMR (Optional element)

Referral for an HMR was not mandated as part of the project. However, in response to learnings from Phases 1 and 2, for GPs who wished to refer patients for HMR as a means to improve their deprescribing capacity, it was requested they would –

- Refer to one of the CPs who attended the deprescribing workshop
- Allow that CP full access to the GP practice record to ensure recommendations could be as informed as possible

6.4.2 Allocation to intervention or control (i.e. usual care)

Allocation to intervention or control (i.e. usual care) was made at a practice level according to the willingness of the GPs in those practices to participate in either the intervention or usual care arm. The small numbers of practices involved precluded conducting a cluster randomised controlled trial (RCT). It was inappropriate for the unit of allocation to be the GP or patient given the potential for contamination effects within practices. That is, patients could not be the unit of randomisation, as the premise of the study was to have the deprescribing appointment with the patient's usual GP and intervention GPs could not 'unknow' what had been learned at the deprescribing workshop. Furthermore, randomisation of GPs within a practice was equally deemed inappropriate, acknowledging that learnings may be shared between colleagues throughout a practice.

6.4.3 Usual Care

Care normally provided by GPs to patients with polypharmacy continued, including referral to specialists, allied health professionals and CPs for HMR. The study was described as a

quality use of medicines activity for community living older patients with polypharmacy to avoid using the term deprescribing which, while used in the intervention sites, did not apply to the usual care sites.

6.5 Outcome and process measures

TABLE 6-2 SUMMARY OF STUDY MEASURES FOR THE MIXED METHODS EXPLORATORY STUDY

Outcome measures pertaining to intervention effectiveness	
Medications	**Primary outcome** - • Mean difference between groups in the number of agreed[a] regular medications deprescribed[b] per patient[c] **Secondary outcomes -** • Proportion of total agreed[a] regular medications deprescribed[b] • Proportions of patients who had ≥1, ≥2, ≥3, or ≥4 medications deprescribed • Mean difference between groups in the number of agreed[a] regular medicines per patient that were[c]- ○ Deprescribed, excluding supplements ○ Ceased ○ Dose reduced ○ Commenced ○ Reconciled • Medication classes most frequently deprescribed[b], ceased and reduced
Patients' self-reported health status and attitudes towards medications and deprescribing	• Worsening of health-related quality of life (HRQoL) as measured by the EQ-5D-5L (202) • Changes in intervention Patients' Attitudes Towards Deprescribing (PATD) as measured by the PATD questionnaire (203)
Unplanned hospitalisations	• Mean number of self-reported[d] unplanned hospital presentations/admissions during the study period
Process measure pertaining to intervention safety	
Patients' or clinicians' report of adverse experiences or outcomes possibly related to the intervention	• Report completion using supplied template (see Appendix 3) as per safety protocol
Outcome measures pertaining to intervention feasibility (adoption, acceptability, sustainability)	

GP/CP service utilisation	• Proportion of patients in the intervention arm who had a deprescribing appointment • Proportion of patients who had an HMR since recruitment to the study • Difference between the mean number GP visits per patient during the study period between the intervention and usual care group
Qualitative measures [e]	GPs' and patients' experiences of implementing the deprescribing intervention, specifically an exploration of views regarding - • Adoption of the interventions' elements (GPs) • Acceptability (GPs and patients) • Sustainability (GPs)

[a] Agreed indicates agreement of the deprescribing change between the GP record and patient-report. Please see further explanation in section 6.5.1.1.1.
[b] Includes ceased and dose-reduced medications.
[c] Corresponding Incidence Rate Ratios (IRRs) were calculated and reported for each of these outcomes
[d] Cross-referencing patient and GP records to confirm details of unplanned hospital presentations/admissions was not possible in every instance due to incomplete GP records. Please see further explanation in section 6.5.2.3.
[e] Constructs of adoption, acceptability and sustainability have been defined using the work by Proctor *et al*. (144) Please see further explanation in section 6.5.3.2.

6.5.1 Effectiveness outcomes - Medication-specific outcome measures

6.5.1.1 Primary outcome

The primary outcome was the mean difference in the number of regular medicines deprescribed per patient for which there was agreement between the GP record and patient self-report at baseline and at study end. 'Deprescribed' was defined as medicines ceased or those which had doses reduced. Dose reduction was included in the definition for two reasons: 1) focus group discussion findings indicated that dose reduction is used by clinicians as a low risk strategy to facilitate medicine cessation, even if weaning the dose was not required pharmacologically (186); and 2) complete cessation may not have been possible within the four-month study period based on the assumption that some medications need to be weaned slowly over several months.

6.5.1.1.1 An explanation for using GP-patient agreed medication lists

The rationale for the use of GP and patient agreed medication lists and changes was related to the pragmatic design of the study. Unlike previously published studies reporting changes to medications, there was no single, reconciled medication list at one or more time points to determine the nature of medication changes over the study period. Developing such a list was not pursued for two reasons: 1) resources were not available to have research staff located across five sites simultaneously to create reconciled medication lists for all study patients; and 2) the intent was for the usual care group to

reflect ‘usual care’ as closely as possible and so it was decided that creating a non-routine opportunity for patients’ GPs to reconcile medication lists – akin to a Hawthorne effect - may lead to review and change of medications that would not otherwise occur under normal circumstances. Medication reconciliation is the first step of the CEASE framework and so creating an opportunity for GPs to do this in the usual care arm would have constituted a form of ‘intervention’.

For this study therefore, the source of truth regarding medications prescribed, and changes made to those medications, were ‘agreed’ medication lists. This comprised medications (and their doses) collected and reported from GP records and patient self-report, at baseline and follow-up, that were totally concordant with each other. These ‘agreed’ lists and changes are what constituted the medication measures reported throughout this and the next chapter. For completeness, GP and patient-reported measures, which may or may not have been concordant, were also separately reported in the relevant appendices. Whilst the approach of presenting GP-patient agreed medication changes had potential to diminish the outcome effect sizes (because it did not account for additional medications/changes that the patient instigated of their own accord or instances of patient non-adherence), it was deemed the most valid way to present the data.

Two additional strategies were employed to account for the use of ‘real-world’ data. Firstly, short course therapies were excluded from the analysis, these being defined as oral and topical antimicrobial therapies at treatment doses, high dose steroids, pain relievers for acute complaints, any medication whose instructions included (‘for x days’) and intra-articular injections. Vaccinations and non-medicated topical therapies were also excluded from the analysis.

Secondly, follow-up medication lists taken from GP records in the intervention group were adjusted for reconciliation, i.e. they were adjusted for changes which occurred simply on paper, as a result of the GP cleaning up or updating the medication record just prior to, or during, the first patient appointment undertaken during the study period. This was done so as not to bias GP-reported outcomes in favour of the intervention, because GPs in the intervention group, unlike usual care prescribers, were afforded the opportunity to reconcile medications at the dedicated deprescribing appointment. The standardised process for adjusting follow-up GP medication lists for reconciliation is detailed in Appendix 9 and the consistency of its application was tested by inter-rater reliability in assessing changes in medication regimens.

6.5.1.1.1.1 Inter-rater reliability in assessing changes in medication regimens

The medication lists of a random sample of 25 patients (13 intervention, 12 usual care) were independently reviewed by the PhD candidate and a research team member, also a pharmacist. This process was undertaken to ensure reliability in the application of the documented process to adjust GP records for medication reconciliation (see Appendix 9). A total of 243 medications were identified by both reviewers as being unchanged and so were not considered as part of the inter-rater reliability task. The rationale for this was that it was assumed that most medications would be unchanged during the study period, and including the unchanged medications in the inter-rater calculations would artificially improve the level of inter-rater agreement. Furthermore, 135 medications were identified by both/either reviewer as having undergone some kind of change during the study period (i.e. ceased, commenced, dose changed, added or removed from the list through reconciliation). In 124 of the 135 instances, there was total agreement between the two raters for both the occurrence and nature of the change, representing 92% agreement (kappa = 0.84).

6.5.1.2 Secondary outcomes

A range of secondary medication-specific outcomes were also specified *a priori*, including the proportion of medications deprescribed as a proportion of total medications between intervention and usual care groups and the proportions of intervention and usual care patients who had at least one, two, three or four or more medications deprescribed. Additional secondary outcomes included the mean difference in the number of agreed regular medications per patient over the study period that were: deprescribed, excluding supplements; ceased; reduced in dose; commenced; and those reconciled (which is step one of the CEASE framework). This range of measures was specified to assess the overall impact and effectiveness of the intervention on the medication regimens of study participants. The medication classes most frequently deprescribed, ceased and to have doses reduced were also reported.

6.5.2 Other effectiveness outcome measures

6.5.2.1 EQ-5D-5L

The *EQ-5D-5L – Telephone interview version* was selected to measure, and assess changes in, health-related quality of life (HRQoL). (202) It consists of five descriptive statements pertaining to five dimensions of health: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. For each dimension, the responses record five levels

of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension. There is also a 100-point 'Visual Analogue Scale', which is adapted for telephone interview, in which a respondent indicates global health. (204) The rationale for including a HRQoL tool in such a short study was as a 'red flag indicator', i.e. to ensure there was not a sudden deterioration in HRQoL associated with imprudent deprescribing attempts by GPs. It was not included to demonstrate a benefit in HRQoL from deprescribing, as literature supports that much longer study periods are generally required to demonstrate such effects from any clinical intervention. (205) The rationale for choosing the EQ-5D-5L was two-fold: 1) its brevity and ability to be easily administered over the phone; and 2) experimental 5-level versions of EQ-5D significantly increase reliability and sensitivity while maintaining feasibility. (204) Although the EQ-5D, like other brief measures of functional status and HRQoL, such as the SF-12, were not originally designed specifically for use in older adult populations, there is evidence of comparable reliability of HRQoL in samples of cognitively intact older adults and adults in general. (204, 206)

6.5.2.2 PATD

In the intervention group, an assessment was made of the change in patients' attitude to deprescribing before and after the intervention using the Patients' Attitudes Towards Deprescribing (PATD) Questionnaire. (203) This tool was selected because, at the time of study design, it was the only survey with demonstrated content validity that was available to assess patients' views of medication appropriateness and burden and their willingness to deprescribe medicines under the supervision of a clinician. (203) Unlike surveys like the Brief Medication Questionnaire, the PATD is not specific to any particular medication class or indication lending itself to an intervention such as the one in the study that focussed on reducing inappropriate medication of any type. A limitation of the PATD is that it has no scoring system. Consequently, although administered in an unaltered way, only the ten first person statements with Likert scales were utilised for analysis, as evidence of item sensitivity, reliability and/or validity was lacking for the remaining items. (203) The authors of the PATD, who published a significantly revised version of the tool in 2016 (207), were contacted to confirm this decision was appropriate. The PATD was only administered to intervention patients to minimise suggestion bias towards deprescribing in usual care participants.

6.5.2.3 Self-reported unplanned hospitalisations

The mean number of self-reported unplanned hospital presentations and admissions during the study period between intervention and usual care patients was reported. This measure was primarily included as another 'red flag indicator' of imprudent deprescribing attempts on the part of either the GPs or patients. Although an attempt was made to cross-reference patient and GP records to confirm details of every unplanned hospital presentation/admission during the study period, this was not possible in every instance due to incomplete GP records. Therefore, in the interest of presenting data in the most valid way, this measure was presented simply as a 'patient self-reported' outcome. Unfortunately, ethics approval had only been sought in advance to verify records with public, not private hospitals, to which many patients presented, so cross-referencing patient-reported presentations/admissions with hospital records was also unviable.

6.5.3 Feasibility outcomes

6.5.3.1 GP/CP service utilisation

The proportion of patients in the intervention arm who had a deprescribing appointment was reported to indicate the level of protocol adherence. Between group differences were also reported at follow-up regarding the mean number of GP visits per patient over the study period and the proportion of patients who had an HMR since recruitment to the study (to determine the relative uptake of this optional element of the intervention).

6.5.3.2 Qualitative measure of the intervention's feasibility

The adoption, acceptability and sustainability of the intervention would be evaluated to determine the feasibility of the intervention. The three aforementioned constructs have been defined using the work by Proctor *et al* (144), such that: adoption is the 'intention, initial decision or action to try or employ an innovation or evidence-based practice'; acceptability is the 'perception among participants that a given treatment, service, practice, or innovation is agreeable, palatable or satisfactory' and; sustainability is 'the extent to which a newly implemented treatment is maintained or institutionalised within a service setting's ongoing, stable operations'.

6.5.4 Safety protocol

As detailed previously, at all times the patient remained under the care of their usual GP and this was clearly articulated to the patients involved in the study. To ensure timely detection and reporting of any actual or suspected adverse consequences arising from deprescribing, GPs were provided with an adverse event reporting form and protocol. See

Appendix 3 for the form to record and report suspected adverse outcomes or experiences to the research team. Patients were, however, also invited to directly contact the research team should they have any non-acute concerns or problems throughout the study period.

6.6 Data collection

6.6.1 Patient telephone survey

Data were collected from the patient via questionnaire completed in an interview-style over the phone at baseline and follow-up. Phone questionnaires were administered by experienced pharmacists (the PhD candidate and two casual research assistants) trained in taking a comprehensive medication history, as per the Australian Commission on Safety and Quality in Healthcare's process to conduct a best possible medication history. (208) Three key measures were taken to ensure a standardised approach to data collection from patients over the phone, including: 1) the development and use of a standardised data collection template and question guide for interviewers (see Appendix 10 data collection form); 2) in-person training of the casual research assistants prior to commencing in the role and again, by phone, after conducting their first three to five interviews; and 3) ensuring, wherever possible, the same individual conducted the baseline and follow-up survey.

In addition to taking a medication history, detailed demographic information such as the country of birth, language spoken at home and pensioner status, which were deemed as variables potentially influencing medication related outcomes, were also collected. All patients were surveyed on their Health-related quality of life (HRQoL) as measured by the EQ-5D-5L at baseline and follow-up. (204) For patients in the intervention arm of the study, the PATD questionnaire was also collected at baseline and follow-up. (203) At follow-up, the number and details of any unplanned hospital presentations/admissions and the occurrence of any HMRs in the six to 12 months prior to, and throughout, the study period were also collected.

6.6.2 Patient data from general practice records

Patient data collected from the medical record at baseline included the patient's age, gender, usual GP, number of regular and prn medications (excluding short-term therapies) and number of documented chronic medical conditions. This latter data was based on the 20 most frequently encountered chronic conditions in primary care in Australia according to the Bettering the Evaluation and Care of Health (BEACH) primary care dataset (209). The process of reviewing the medical record until saturation was reached was used for this

data collection (that is, active and past medical conditions, hospital discharge and specialist letters and other relevant documents in the file were reviewed until no new documented chronic diagnoses could be found).

At baseline and follow-up, data were collected on: the frequency and details of GP appointments during the study period; the number and details of any HMRs in the 12 months prior to recruitment and during the study period; and the number and details of any unplanned hospital presentations or admissions six months prior to and throughout the study period (where available).

For intervention patients at follow-up, data were also collected on: completion of the deprescribing consultation template by GPs in the intervention arm; and details of any deprescribing decisions/outcomes.

6.6.3 Baseline practice and clinician level data collected by survey

At baseline, basic descriptive data were collected from practices and clinicians to provide essential context to the study. Practices completed brief surveys to provide information regarding staffing and co-located services. Clinicians completed surveys to provide basic demographic information and details regarding their experience and work status (e.g. part-time or full-time work status). Copies of the data collection forms are contained in Appendix 11 and Appendix 12.

6.6.4 Qualitative data

Qualitative data were used to examine feasibility of the intervention and to help explain and contextualise the quantitative findings. At completion of the study, in-depth face-to-face semi-structured interviews were conducted with all 10 intervention GPs. Interviews were on average 29 minutes in duration, range 15-51 minutes. By comparison, much briefer interviews (average duration 6 mins, range 1.5-16 minutes) were conducted with a convenience sample of 52 intervention patients by telephone (determined by those willing to have their responses audio recorded at the end of the follow-up phone survey for verbatim transcription at a later point). The patient interviews were conducted by the PhD candidate and one of the research assistants who underwent additional training in the technique of conducting semi-structured interviews.

As the primary adopters of the intervention, the key focus of interviews with GPs was to explore the: 1) adoption of the elements of the intervention (i.e. identifying potentially eligible patients, participating in the deprescribing training workshop and having at least one

extended deprescribing appointment with their patients); 2) acceptability of the intervention; and 3) likelihood of sustainability of deprescribing in routine care, including future commitment and resource requirements required to facilitate this. In contrast, the primary focus of interviews with patients, as secondary adopters of the intervention was their perceived acceptability of the deprescribing appointment/s with their GP.

All topics were explored both generally and specifically with each participant, by the interviewer raising examples of relevant positive and negative deprescribing outcomes and experiences throughout each interview. The interview guides for the intervention GPs and patients are included in Appendix 13 and Appendix 10 (as part of the Intervention patient follow-up data collection form), respectively.

6.6.5 Follow-up period

The median follow-up period was 125 days (IQR = 118-132.5, full range = 86-198) and 126 days (IQR = 124-129, full range = 123-132) days for the intervention and usual care groups, respectively. The date range was wider for the intervention group because each patient had their own individual timeline determined by the date of their initial deprescribing appointment, and it was impractical to return to the practice to collect follow-up data for each person individually at a uniform time after this appointment. Rather, the date for follow-up data collection was determined for each GP, and was approximately four months from the midpoint of all of his or her initial deprescribing appointments. All baseline phone interviews with intervention patients occurred prior to their deprescribing appointments. Appendix 14 provides more detail of the exact timing of data collection.

6.7 Data analyses

6.7.1 Between group differences at baseline

The characteristics of intervention and usual care patients and GPs were reported at baseline. For non-normally distributed continuous or ordinal variables, medians and interquartile (IQR) ranges were reported. For normally distributed continuous variables, the mean (standard deviation [SD]) was reported. The following tests were employed to check for statistically significant differences between groups using two-sided criteria and alpha of 0.05 -

1. Independent samples t-test and Mann-Whitney U Test, for continuous variables which were normally and non-normally distributed, respectively

2. Chi-square test for Independence for categorical variables or Fisher's exact test in instances where cells had expected counts less than five (as occurred in several instances when comparing the characteristics of GPs)

6.7.2 Outcomes pertaining to medication changes

Analyses were conducted on the intent-to-treat (ITT) basis. Applying the ITT principle refers to undertaking the analysis according to the allocation to, rather than actual receipt of, the intervention by the study participants and is undertaken to minimise bias introduced by excluding patients who are non-adherent to the study protocol. (210) Empirical evidence suggests that non-adherent patients invariably have worse outcomes than adherent patients and so the exclusion of non-adherent patients may otherwise artificially improve controlled study outcomes.(210)

As the primary and secondary outcomes pertaining to differences in the mean number of medication changes per patient were non-normally distributed counts, Negative binomial or Poisson regression was used depending upon the variance-to-mean ratio (i.e. if the variance to mean ratio >1.5, Negative binomial regression was used, as is convention). A description of variables tested in the General Linear Modelling as possible predictors of the primary outcome is detailed in Table 6-3.

TABLE 6-3 DESCRIPTION OF COVARIATES AND FACTORS TESTED IN THE GENERAL LINEAR MODELLING AS PREDICTORS OF THE PRIMARY OUTCOME

Variable	Variable type	Description of categories [a]	Statistically significant? Y/N
Age (in years)	Continuous	N/A	N
Gender	Categorical	Female; Male.	N
Allocation to intervention	Categorical	Usual care (reference); Intervention.	Y
Number of regular baseline medications[b]	Continuous	N/A	Y
Medications packed by pharmacy at baseline (e.g. Webster® pack or sachets)	Categorical	Yes or No	N
Self-managing medicines (i.e. responsibility of medication management not devolved to carer)	Categorical	Yes or No	N
Baseline PATD scores	Continuous	N/A	N
General Practice	Categorical	1,2,3,4,5.	N

[a]For categorical variables the first category listed was used as the reference value.
[b]The source for the number of regular baseline medications imputed into the model was consistent with the outcome to be reported. For example, for an 'agreed' medication outcome, the 'agreed' number of baseline regular medications was used, for a patient-reported medication outcome, the patient reported number of baseline regular medications was used etc. Exploration of the data did not show a change in the statistical significance of medication outcomes when the number of baseline medications from another source were tested.

Apart from age and gender, only allocation to intervention and the number of regular baseline medications were statistically significant (p value <0.05) predictors of the primary (and secondary) outcome/s, and so were retained in the main effects Generalised Linear Model. Effect estimates from the model's output were reported as Incidence Rate Ratios (IRRs).

Given the exploratory nature of this study, in the regression analysis, associations between the primary outcome and pre-specified criteria were also undertaken, such as the association between the number of baseline medications and the number of medicines deprescribed per patient. The impact of HMR services on the primary outcome were also examined.

Given that the outcomes pertaining to medication changes were non-normally distributed counts, usual statistical convention would be to report the change in the median number of medications per person with the inter-quartile range (IQR). The distribution of the data (the large number of 'zeros' and low kurtosis) meant that the mean proved to be the better descriptor of central tendency (as the median was too limited by its small range).

A per-protocol sensitivity analysis was also specified *a priori*.(210) Additional post-hoc sensitivity analyses were undertaken for patients of two GPs who breached the recruitment protocol and for the patients of one GP who left the practice during the study period. See section 7.2 'Adherence to protocol' for more detail.

In reporting between group differences at follow-up (e.g. the proportion of patients with one, two, three or four or more medications deprescribed), the Chi square-test for Independence (or Fisher's exact test in instances where cells had expected counts less than five) was employed to check for statistically significant differences between groups using two-sided criteria and alpha of 0.05.

6.7.3 Measures pertaining to patients' self-reported health status and attitudes towards medications and deprescribing

6.7.3.1 EQ-5D-5L

Given the use of the EQ-5D-5L as a 'red flag indicator' of worse HRQoL over the study period, the five levels of the first five domains were each converted to a dichotomous outcome for analysis – outcome worse or not. There is precedent for dichotomising the EQ-5D-5L domains in this way. (204) The Chi-squared test for independence (with Yates Continuity Correction) using two-sided criteria and an alpha of 0.05 were used to analyse

the dichotomised outcomes. A dependent samples t-test using single-sided criteria and alpha of 0.05 was used to test for statistically significant differences in the EQ-VAS.

6.7.3.2 PATD

The PATD scores were used for two purposes:

1. To investigate if baseline responses were predictive of the primary outcome; and
2. To investigate what changes, if any, occurred in PATD scores for the intervention group between baseline and follow-up.

6.7.3.2.1 Approach taken to investigate if baseline responses were predictive of the primary outcome

As there is no cumulative score for the PATD or its first ten items, Principal Components Factor Analysis was conducted for each of the 10 items of the PATD. The goal of Factor Analysis is to identify underlying variables, or factors, that explain the pattern of correlations within a set of observed variables. It is often used in data reduction to identify a small number of factors which explain most of the variance observed in a larger number of variables.(211) Extraction was based on Eigenvalues greater than 1 and the Varimax Method of Rotation was used. There is the potential for factor analysis to generate more factors than are actually present by chance for ordinal data. Therefore, two criteria were specified to ensure confidence in the interpretation and naming of items: (212)

1. Only items with high factor loadings (i.e. conventionally defined as coefficients > 0.5 in exploratory Factor Analysis) were retained; and
2. Items were checked to ensure factors for which they had high loadings represented similar aspects of the phenonemnon of interest.

6.7.3.2.2 Approach taken to investigate what changes, if any, occurred in PATD scores for the intervention group between baseline and follow-up

The Wilcoxon signed-rank test was used to test for statistically significant changes in each of the ten PATD items using two-sided criteria and an alpha of 0.05.

6.7.4 Measures pertaining to unplanned self-reported hospitalisations and GP/CP health service utilisation

Poisson regression modelling adjusting for age, gender, number of GP-patient agreed regular medications at baseline and number of common chronic comorbidities was used to test for statistically significant differences between the number of self-reported unplanned hospitalisations during the study period between intervention and usual care patients.

An independent samples T-test was used to test for statistically significant differences in the number of GP appointments and HMRs between intervention and usual care patients using two-sided criteria and an alpha of 0.05.

6.7.5 Statistical analysis

IBM SPSS Statistics Version 24, 2016, was used for all quantitative statistical analyses. (213)

6.7.6 Qualitative analysis

A qualitative descriptive approach was used for this investigation. This has been shown to be an appropriate choice for mixed methods health services research, particularly when the purpose is to gain firsthand insight into participants' experience of a newly adopted treatment, service or practice. (142) Using the Framework approach, thematic analysis was conducted deductively initially, with responses segmented according to interview questions which aligned with the intervention phases.(214) The second step involved developing themes inductively, with reference to concepts from the feasibility study literature. (215) Whilst both GP and patient data sets were analysed separately initially to explicate the main themes and contrasts within these themes from each viewpoint, an integrated GP and patient perspective was elicited regarding the acceptability of the deprescribing appointment/s, as this was the one element of the intervention common to both adopters.

6.8 Conclusion

This chapter details the methods used for the Phase 3 exploratory mixed methods study. Quantitative results of this exploratory study will be presented next in Chapter 7. Chapter 8 will present findings of the qualitative aspect of the intervention.

Chapter 7 Quantitative results of Phase 3 exploratory study

The third thesis aim was to test the feasibility, effectiveness and safety of a multifaceted intervention to facilitate GP-led deprescribing in community living older people in primary care. The quantitative results pertaining to the adoption and effectiveness of the intervention are presented in this chapter. Specifically, the extent of uptake of the intervention (including protocol adherence) and its effect on the medication regimens of older people are reported. As detailed in the preceding chapter, the primary outcome was the mean difference in the number of regular medicines deprescribed per patient for which there was total agreement between the GP record and patient self-report. The use of 'agreed' medication changes for the primary and secondary outcome measures in this chapter reflects an innovative solution to the data quality issues encountered in this pragmatic study. For each of the agreed outcomes reported, GP- and patient- reported outcomes are also presented separately in the relevant appendices. It is to be noted that data from GP records were adjusted for reconciliation using a standardised process detailed in Appendix 9. This was done so as not to bias GP reported outcomes in favour of the intervention group, whose GPs were afforded the opportunity for medication reconciliation (i.e. deleting, adding or changing the dose of previously listed medications) at the deprescribing appointment, in contrast to usual care GPs and their patients. As it turned out, this adjustment had no effect on the GP-patient agreed outcomes, but it ensured that, when reviewing the changes according to the GP-record, the effect size of outcomes was not artificially inflated for the intervention group simply because of reconciliation.

In reporting the medication outcomes, the use of the mean, rather than the median is not usual statistical convention for non-normally distributed counts. However, in this circumstance, it proved the best measure of central tendency due to low kurtosis in the dataset. Therefore, mean differences have been reported for all medication-specific outcomes but, in the interest of completeness, both the mean and median have been reported for each outcome in the tables throughout this chapter. The chapter concludes with the presentation of data regarding the impact of the intervention on patients' attitudes towards deprescribing, their medication regimens and self-reported quality of life.

7.1 Study setting

7.1.1 General practice sites

Five practices agreed to participate in the study; three as intervention sites, two as usual care sites. All five practices were accredited with Australian General Practice Accreditation Ltd and owned by one or more GPs working in the practice. Four of the five practices used Best Practice® Medical Software and one used Medical Director®. Information about GP and nursing staffing levels, the proportion of older people who attended the practice and the number of GPs and patients enrolled per site is presented in Table 7-1.

TABLE 7-1 DESCRIPTIVE INFORMATION FOR EACH OF THE GENERAL PRACTICE SITES

GP PRACTICE	FTE GPs	FTE RNs	FTE ENs	% active[a] patients aged ≥65 years	GPs enrolled from site	GP head count per site	Patients enrolled from site[b]
Intervention 1	6	2	0	17%	3	10	25
Intervention 2	10	3	0.25	19%	3	12	34
Intervention 3	6.5	3	0	14%	4	13	23
Usual Care 1	5	1.25	0	20%	4	7	29
Usual Care 2	8	3	1	14%	6	12	44

FTE= Full Time Equivalent; GP = General Practitioner; RN = Registered Nurse; EN = Enrolled nurse.
[a]In accordance with the RACGP definition, an active patient was defined as a person who had attended the practice/service three or more times in the two years preceding enrolment. Full-time equivalence was defined as working a minimum of 38 hours per week.
[b]Note this refers to patients enrolled, not recruited, to the study from each site. See Figure 7-1 for detail.

Practices involved in the study tended to be large practices that serviced a comparable proportion of patients aged 65 years and older. All were mixed billing practices, with policies to bulk-bill children, aged pensioners and concession card holders. Bulk-billing is where a practice directly bills Medicare for a health service and does not charge the patient an out-of-pocket fee. There was one exception - one site charged a nominal out-of-pocket fee for aged and disability pensioners and concession card holders to limit service demand, but this could be waived at the doctor's discretion.

Between three and four GPs were recruited per site, with the exception of the fifth practice where six GPs agreed to participate as part of the usual care group. All practices had one or more full time equivalent registered nurses (RNs) incorporated within the practice and all practices engaged nursing staff for management of patients with chronic disease (for example all used nursing staff to assist in conducting federally-funded Health Assessments). All but one site had one or more allied health professionals operating out of rooms of the practice. Only one intervention site practice had a consultant pharmacist

(CP) engaged as a non-dispensing practice pharmacist. This pharmacist was recruited to the study and attended the deprescribing workshop. It should be noted however that prior to the study, only one of the three GPs recruited to the study from that site had engaged this pharmacist to conduct any Home Medicines Reviews (HMRs).

7.1.2 Participants

7.1.2.1 General practitioners

Twenty GPs enrolled in the study – 10 each in the usual care and intervention groups. The baseline characteristics of the GPs are displayed in Table 7-2. There were no significant differences between GPs in the intervention and usual care groups of the study. The age and experience range for GPs in the intervention and usual care groups were comparable. With the exception of three intervention GPs, all GPs had attained their medical qualifications in Australia.

TABLE 7-2 BASELINE DOCTOR CHARACTERISTICS

Characteristic	**Intervention (n = 10)**	**Usual care (n = 10)**	**P value[a]**
Mean (SD) age in years	49.6 (13.492)	54.1 (10.461)	0.415[b]
Female (%)	50%	50%	1.000
Mean (SD) number of years registered as a GP	20.6 (15.735)	23.7 (14.743)	0.655[b]
Australia as country of qualification (%)	70%	100%	0.211
Full Time status (defined as 38 hours or more direct patient hours per week) (%)	50%	60%	1.000
Median (IQR) number of patients per GP recruited to the study	9.50 (4.25-11.00)	6.00 (4.75-9.50)	0.493

[a]Two tailed. [b]Result no different if equal variances not assumed.

7.1.2.2 Consultant pharmacists

Two CPs were recruited to the study as it was determined that this number would be adequate to perform HMRs for Intervention patients should GPs wish to refer them for HMR during the study period. Both were female, qualified in Australia and had worked as consultant pharmacists for 18 and 19 years, respectively. As stated above, one of these CPs was working as the practice pharmacist for one of the intervention sites. The second CP was external to the other two intervention sites and met the GPs for the first time at the deprescribing workshop.

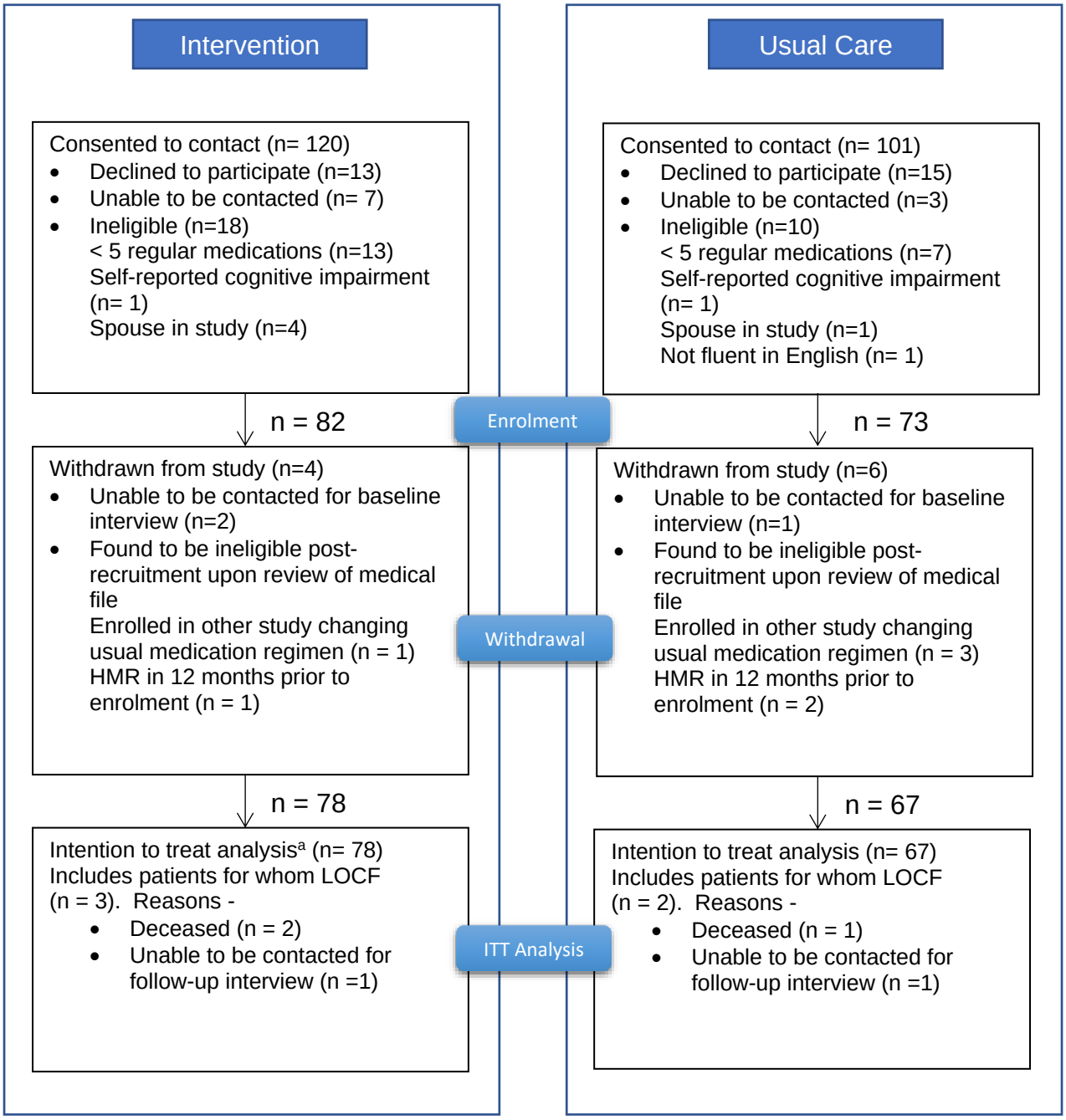
7.1.2.3 Patients

Of the 153 patients enrolled in the study, 145 were included in the analysis; 78 in the intervention group and 67 in the usual care group. Figure 7-1 shows a flow diagram of patient enrolment and analysis. Reasons for non-enrolment and withdrawal from the study

have been provided. The main reason for ineligibility was that patients were taking fewer than five prescribed medications regularly (as opposed to prn medications) at the time of enrolment despite practice records indicating otherwise. During phone recruitment of patients, 'regularly' was defined as 'on a daily basis' to provide clarity. A level of discordance between what the patient was taking and what was listed on the general practice record was expected as this has been reported repeatedly in previous studies.(200, 216). Note that 'prescribed' medications also included supplements or OTC medications which were prescribed or at the very least noted in the medical record by the GPs, e.g. calcium/vitamin D supplements or paracetamol, but which did not necessarily require a written prescription.

Some patients initially enrolled in the study were in fact ineligible. This was only learned during the data collection process because, to preserve confidentiality, full patient details were not available prior to receipt of informed consent from individual patients. Three enrolled individuals were withdrawn from the study as they were unable to be contacted for a baseline interview.

FIGURE 7-1 FLOW DIAGRAM OF PATIENT ENROLMENT AND ANALYSIS IN THE EXPLORATORY STUDY



[a]In the intention to treat analysis, three patients (including one deceased patient) in the intervention group did **not** have a deprescribing appointment with their GP. LOCF=last observation carried forward

Patients in the intervention and usual care groups demonstrated similar characteristics at baseline, as seen in Table 7-3.

TABLE 7-3 BASELINE PATIENT CHARACTERISTICS

Characteristic	Intervention (n= 78)	Usual care (n = 67)	P value (2-tailed)
Median age in years (IQR)	74 (69.75, 80.25)	77 (70.00, 82.00)	0.189
Male (%)	41.0	32.8	0.309
Residing alone (%)	32.1	37.3	0.506
Self-managing medications (%) (i.e. Responsibility not devolved to a carer)	89.6	89.2	0.942
Median (IQR) number of most common chronic conditions per patient (as per BEACH[a] list)	5 (4-7)	5 (4-7)	0.958
Condition frequency (%)			
Hypertension	82.1	83.6	0.808
Hyperlipidaemia	57.7	56.7	0.906
GORD	51.3	43.3	0.336
Ischaemic heart disease	39.7	55.2	0.063
Osteoarthritis	44.9	46.3	0.866
Type 2 Diabetes	42.3	28.4	0.081
Depression	33.3	22.4	0.145
Asthma	25.6	25.4	0.971
Chronic back pain	24.4	20.9	0.620
Osteoporosis	23.1	20.9	0.752
Median (IQR) number of agreed[b] baseline **regular** medications per patient, excl. short course therapies [c]	8 (6-10)	9 (6-10)	0.427
% of patients taking top 10 most frequently occurring medication classes of all baseline medication classes			
Statin	70.5	62.7	0.318
Supplement – single ingredient [d]	37.2[e]	46.3[e]	0.268
PPI or H2 antagonist	62.8	53.7	0.268
Antiplatelet	52.6	55.2	0.749
AT2RB	48.7	37.3	0.167
Oral hypoglycaemic	30.8	20.9	0.178
Beta-blocker	42.3	38.8	0.669
Calcium channel blocker	41.0	43.3	0.784
Diuretic	33.3	29.9	0.653
Other[f]	17.9	19.4	0.823
Median number of agreed[a] baseline **prn** medications, excl. short-term therapies	1 (0-2)	1 (0-2)	0.140
% of people for whom English is usual language spoken at home	97.4	98.5	1.000

[a]BEACH refers to the Bettering the Evaluation and Care of Health dataset from primary care in which the most frequently encountered chronic conditions in primary care in Australia are detailed. (209)

[b]Agreed indicates medications at baseline for which there was total agreement between the GP record and patient-self report.
[c] Short course therapies included oral and topical antimicrobial therapies at treatment doses, high dose steroids, pain relievers for documented/reported acute complaints, any medication whose instructions include ('for x days'), intra-articular injections, vaccinations, non-medicated creams.
[d]'Supplements – single ingredient' included a range of vitamin, mineral and complementary medications, the top five of which in descending count order were Vit D, Vit B12 injections, fish oil, folic acid and calcium.
[e] Note that some patients were taking multiple medications within the one class (e.g. supplement – single ingredients).
[f]'Other' in usual care arm: acyclovir, anastrozole, baclofen, bortezomib injection, calcitriol, darbepoetin, dutasteride, famciclovir, filgrastim injection, finasteride, fluconazole, imatinib, IV immunoglobulins, nicorandil x 3, potassium binding resin, pyridostigmine, sulfasalazine, tamsulosin, tranexamic acid, valacyclovir.
'Other' in intervention arm: betahistine, calcitriol, dutasteride x 3, goserelin implant, lomotil, mebeverine, melatonin x 2, nicorandil x 3, norgesic, prazosin, quinine, ranibizumab eye injection, tamsulosin x 3, zopiclone.

The documented prevalence of chronic conditions most commonly encountered in general practice was the same between the groups. Prevalence of ischaemic heart disease in the intervention group compared to the usual care group was somewhat lower (39.7% vs 55.2%, two-sided p-value 0.063) while prevalence of type 2 diabetes was somewhat higher (42.3 % vs 28.4%, two-sided p-value 0.081). The proportion of patients taking one or more medications from the top 10 most frequently occurring medication classes at baseline did not differ between the intervention and usual care group.

7.2 Adherence to protocol

Two of the 10 intervention GPs reported a protocol breach in the generation of a sample of patients for recruitment to the study. The first GP admitted that he did not open the patient files when reviewing his patient list generated from the software query to confirm each was taking the minimum required number of regular medications according to the software. Rather, this GP reviewed their list and identified patients who, from memory, were taking 'a large number of medications'. The second GP advised that he screened his patients according to the perceived willingness of the patient to firstly agree to participate in the study and secondly, to be compliant with the intervention. His rationale was that he was not aware of the criteria to generate a consecutive sample of patients. A sensitivity analysis excluding the patients of these two GPs was conducted to examine what effect, if any, these protocol breaches had on the primary outcome (see 7.4.3 for more detail).

All 10 intervention GPs attended one of the two five-hour deprescribing training workshops. A total of 75 of 78 (96.2%) intervention patients had an initial deprescribing appointment with their GP as scheduled. One of the three patients who did not have a deprescribing

appointment died before this was able to be scheduled. The remaining two patients provided reasons for declining an appointment when approached by the practice as planned. The first patient described the busyness of their work schedule and general sense that the appointment was probably unnecessary as their GP would identify any medication related issues through usual care. The second patient misunderstood the study protocol, and declined an appointment with their usual GP, as they thought this was to occur with the research team.

In regard to the use of the autofill template to document the GP-patient deprescribing appointment/s, all but one of the 10 GPs used the autofill template, and this individual could not provide an explanation for her non-use. For the remaining GPs, there was a high degree of variability in the level of detail and content captured in the autofill template. None of the GPs continued to use the autofill template for documentation beyond the study period, but this was expected as the template was study specific (the first line of the template to pre-populate the consult notes was, “Patient presented as part of the UQ study on deprescribing”). Some GPs did, however, report continuing to use the reasons for ceasing medications when changing the ‘Current Medication’ list, which remained available as a dropdown menu when making changes to medications in the medical software.

7.3 Feasibility outcomes

7.3.1 GP/CP utilisation

An independent samples T-test showed there was no significant difference in the mean [SD] number of GP appointments per patient in the intervention compared to the usual care group (4.88 [2.512] and 4.46 [2.625] appointments respectively, p = 0.325) during the study period which averaged four months. The median (IQR) length of the initial deprescribing appointment for intervention patients was 32 (21-46) minutes. All but two of the 75 deprescribing appointments were bulk-billed.

For the 75 intervention and 65 usual care patients for whom GP and patient-reported follow-up data were available, 10 (13.3%) intervention patients and three (4.6%) usual care patients had had an HMR since being recruited to the study. In the intervention group, all ten referrals came from two GPs at the site at which the CP was co-located, although interestingly, they had not engaged the services of this pharmacist prior to the study. There was no significant

association between an HMR having been performed following a patient's recruitment to the study and assignment to the intervention.

7.4 Effectiveness outcomes – Medication-specific outcomes

7.4.1 Primary outcome

In terms of the primary outcome, the mean difference between intervention and usual care groups in the number of regular medications deprescribed (i.e. ceased or reduced) per patient was -0.55, 95%CI -0.897 to -0.212, p = 0.002, see Table 7-4. Crude totals showed 77 of 649 (11.9%) baseline regular medications in the intervention group were deprescribed compared to 29 of 571 (5.1%) corresponding medications in the usual care group over the 18 week study period (p<0.001).

7.4.2 Secondary outcomes

The proportion of patients in the intervention group who had at least one medication deprescribed was 52.6% versus 28.4% in the usual care group (p=0.005). In comparison with the usual care group, intervention group patients were 2.3 times more likely to have at least one regular medication deprescribed (i.e. ceased or reduced) during the study period (incidence rate ratio [IRR] 2.3; 95% CI 1.297 to 3.964, p = 0.004). The respective proportions of intervention and usual care patients who had two or more medications deprescribed were 26.9% vs 9.0% (p=0.011), for three or more medications 11.5% vs 4.5% (p=0.143) and for four or more medications 6.4% vs 1.5% (p=0.217).

A statistically significant correlation was apparent between the number of regular medications at baseline and the likelihood of deprescribing. The output from the Negative binomial regression modelling showed that for every additional regular medication prescribed at baseline, the likelihood of having one or more medications deprescribed increased by 16.5% (IRR = 1.165, 95% CI 1.074 to 1.263, p < 0.001).

TABLE 7-4 AGREED[A] GP AND PATIENT-REPORTED CHANGES TO REGULAR MEDICATIONS PER PATIENT DURING THE STUDY PERIOD FOR INTERVENTION AND USUAL CARE GROUPS

Outcome	Measure of central tendency	Intervention (SD) N=78	Usual Care (SD) N=67	Mean Difference (95% CI)[c]	IRR[d] (95%CI)	P value
Primary Outcome - Deprescribed[b]						
Deprescribed[b]	Mean	0.99 (1.233)	0.43 (0.839)	-0.554 (-0.897- -0.212)	2.267 (1.297-3.964)	0.004
	Median	1 (0-2)	0 (0-1)			
Deprescribed[b] excluding supplements	Mean	0.81 (1.058)	0.42 (0.781)	-0.390 (-0.693- -0.087)	1.915 (1.087-3.374)	0.025
	Median	0 (0-1)	0 (0-1)			
Secondary Outcomes						
Ceased	Mean	0.62 (1.022)	0.25 (0.682)	-0.362 (-0.644- -0.080)	2.490 (1.255-4.938)	0.009
	Median	0 (0-1)	0 (0-0)			
Reduced[e]	Mean	0.37 (0.686)	0.18 (0.490)	-0.193 (-0.387- 0.001)	2.011 (1.023-3.954)	0.043[f]
	Median	0 (0-1)	0 (0-0)			
Commenced	Mean	0.24 (0.488)	0.30 (0.798)	0.055 (-0.159- 0.269)	0.839 (0.407-1.730)	0.635
	Median	0 (0-0)	0 (0-0)			
Increased[e]	Mean	0.09 (0.288)	0.10 (0.308)	0.015 (-0.83- 0.113)	0.791 (0.277-2.263)	0.662[f]
	Median	0 (0-0)	0 (0-0)			

[a] Agreed indicates agreement of the deprescribing change between the GP record and patient-report.
[b] Includes ceased and dose-reduced medications.
[c] Equal variances not assumed if p-value for Levene's Test for Equality of Variances was <0.05.
[d] IRR - Incidence Rate Ratio (adjusted for number of baseline regular medications, age and gender).
[e]Poisson used instead of Negative binomial regression as variance:mean <1.5.
[f]Note that the number of baseline medications did not remain a statistically significant predictor in the model.

When comparing patients taking up to nine medications at baseline to patients taking 10 or more regular medications at baseline (i.e. hyperpolypharmacy), the latter group were 2.5 times more likely to have a medication deprescribed, IRR 2.5, 95% CI 1.422 to 4.376, p = 0.001. A three-way cross-tabulation and Chi-square test showed that significantly more patients with hyperpolypharmacy in the intervention group had at least one medication deprescribed (16 of 21 [76%] of patients) compared with similar patients in the usual care group (9 of 25 [36%] of patients), 2-sided p = 0.006. Table 7-5 shows a breakdown of the

number of medications deprescribed across both intervention and usual care groups according to baseline number of regular medications for each patient.

TABLE 7-5 CROSS-TABULATION OF THE NUMBER OF MEDICATIONS DEPRESCRIBED OVER THE STUDY PERIOD ACCORDING TO THE NUMBER OF BASELINE MEDICATIONS FOR EACH STUDY GROUP

Study group	Baseline medications (abbreviated to 'meds')	Number of medications deprescribed over study period						
		0	1	2	3	4	5	Total
Usual care (n = 67)	<9 baseline meds	32	8	1	1	0		42
	≥10 baseline meds	16	5	2	1	1		25
	Total	48	13	3	2	1		67
Intervention (n = 78)	<9 baseline meds	32	15	7	3	0	0	57
	≥10 baseline meds	5	5	5	1	4	1	21
	Total	37	20	12	4	4	1	78

As detailed in Table 7-6, single ingredient supplements (e.g. Vit B12 injections, oral calcium, fish oil, folic acid, slow-release potassium) were the medications most commonly deprescribed in the intervention group (12 out of 77 [15.6%] medications deprescribed), followed by proton pump inhibitors (PPI) and H2 antagonists (8 of 77 [10.4%]), statins (8 of 77 [10.4%]), oral hypoglycaemics (7 of 77 [9.1%]) and diuretics (5 of 77 [6.5%]). In the usual care group, the medications most commonly deprescribed were calcium channel blockers (5 of 29 [17.2%]), anticonvulsants (4 of 29 [13.8%]) and antiplatelet agents (4 of 29 [13.8%]).

Having an HMR following recruitment to the study was not shown to have a statistically significant effect on the primary outcome of agreed medications deprescribed during the study period when tested in regression modelling (IRR for HMR following recruitment to study 0.8, 95% CI 0.311 to 2.185, p = 0.698).

7.4.2.1 Medications that were deprescribed, excluding supplements

When all supplements (single- or multi- ingredient) were excluded, this equated to a decrease in the mean (SD) number of regular medications deprescribed per patient from 0.81 (1.058) to 0.42 (0.781) in the intervention and usual care groups respectively, with the mean difference being -0.390 (95%CI -0.693 to -0.087, p = 0.012), an effect that remained statistically significant with an IRR of 1.9 (95% CI 1.087 to 3.374, p = 0.025). Crude totals showed 63 of 584 (10.8 %) non-supplement medications in the intervention group were

deprescribed compared to 28 of 501 (5.6%) in the usual care group over the 18 week study period (p = 0.002).

Considering medications deprescribed according to either the GP record or patient-self report as the source of truth, the primary outcome, including and excluding supplements, remained statistically significant. See Appendix 15 and Appendix 16.

TABLE 7-6 REGULAR MEDICATIONS DEPRESCRIBED FOR WHICH THERE WAS GP AND PATIENT AGREEMENT

Medication Class	Frequency	Percent	Cumulative Percent
Usual Care			
Calcium channel blocker	5	17.2	17.2
Anticonvulsant	4	13.8	31.0
Antiplatelet	4	13.8	44.8
Diuretic	2	6.9	51.7
PPI or H2 antagonist	2	6.9	58.6
AT2RB	1	3.4	62.1
Beta-blocker	1	3.4	65.5
Immune suppressant	1	3.4	69.0
Insulin	1	3.4	72.4
Long-term antibiotic	1	3.4	75.9
NSAID	1	3.4	79.3
Opioid analgesic	1	3.4	82.8
Other	1	3.4	86.2
Other antihypertensive	1	3.4	89.7
Statin	1	3.4	93.1
Supplement - multiple ingredient	1	3.4	96.6
TCA	1	3.4	100.0
Total	**29**	**100.0**	
Intervention			
Supplement - single ingredient	12	15.6	15.6
PPI or H2 antagonist	8	10.4	26.0
Statin	8	10.4	36.4
Oral hypoglycaemic	7	9.1	45.5
Diuretic	5	6.5	51.9
Other	5	6.5	58.4
Bisphosphonates	4	5.2	63.6
AT2RB	3	3.9	67.5
Calcium channel blocker	3	3.9	71.4
SSRI/SNRI	3	3.9	75.3
Anticonvulsant	2	2.6	77.9
NSAID	2	2.6	80.5
Supplement - multiple ingredient	2	2.6	83.1
Allopurinol	1	1.3	84.4

Anticoagulant	1	1.3	85.7
Antiplatelet	1	1.3	87.0
Beta-blocker	1	1.3	88.3
Immune suppressant	1	1.3	89.6
Inhaled beta-agonist	1	1.3	90.9
Inhaled combination product	1	1.3	92.2
Inhaled muscarinic antagonist	1	1.3	93.5
Insulin	1	1.3	94.8
Oral corticosteroid	1	1.3	96.1
Other antilipidaemic	1	1.3	97.4
Paracetamol	1	1.3	98.7
TCA	1	1.3	100.0
Total	**77**	**100.0**	

Other intervention – zopiclone, norgesic, tamsulosin (as duodart), calcitriol, melatonin SR

Other usual care – sulfasalazine

7.4.2.2 Medications that were ceased

In comparison with the usual care group, intervention group patients were 2.5 times more likely to have at least one regular medication ceased during the study period (IRR 2.5, 95% CI 1.255 to 4.938, p = 0.009) such that the mean difference between groups was -0.362 medications, 95% CI -0.644 to -0.080, p= 0.012.

A statistically significant relationship was apparent between the number of regular medications at baseline and the likelihood of having one or more medications ceased. The output from the Negative binomial regression modelling showed that for every additional regular medication at baseline, the likelihood of having one or more medications ceased increased by 25% (IRR 1.25, 95% CI 1.135 to 1.377, p = < 0.001).

As detailed in Table 7-7, single-ingredient supplements (12 of 48 [25%]), diuretics (5 of 48 [10.4%]), bisphosphonates (4 of 48 [8.3%]) and oral hypoglycaemics (4 of 48 [8.3%]) were the classes of medications most commonly ceased in intervention group patients. In the usual care group, the medications most commonly ceased were calcium channel blockers (4 of 17 [23.5%]), anti-platelets (3 of 17 [17.6%]) and diuretics (2 of 17 [11.8%]).

7.4.2.3 Medications that were dose reduced

In comparison with the usual care group, intervention group patients were 2.0 times more likely to have the dose of at least one regular medication reduced during the study period

(IRR 2.0, 95% CI 1.023 to 3.954, p = 0.043) such that the mean difference between groups was -0.193 medications 95% CI -0.387 to 0.001, p= 0.051.

Table 7-8 shows that statins (9 of 33 [27.3%]) and PPI or H2 antagonsists (7 of 33 [21.2%]) were the medication classes most likely to have doses reduced in the intervention group during the study period. In the usual care group, anticonvulsants were the medication class most likely to have doses reduced (3 of 8 [37.5%]). The number of regular medications at baseline was not a statistically significant predictor of medication/s reduced in the regression modelling.

7.4.2.4 Medications that were commenced or dose increased

As detailed in Table 7-4, there was no statistically significant difference in the number of regular medications commenced or to have doses increased between groups during the study period: medications commenced (IRR 0.8, 95%CI 0.407 to 1.730, p = 0.635); medications with doses increased (IRR 0.8, 95%CI 0.277 to 2.263, p = 0.662). Similarly, there was no statistically significant difference in the number of prn medications started between intervention and usual care patients (IRR 0.957, 95%CI 0.129 to -7.112, p = 0.965).

Consistent with the primary outcome, when GP and patient-reported changes were considered separately, corresponding secondary outcomes remained statistically significant. The few exceptions to this were for the outcomes of ceased medications when supplements were excluded from the analysis and patient-reported dose-reduced medicines. See Appendix 15 and Appendix 16.

TABLE 7-7 REGULAR MEDICATIONS CEASED FOR WHICH THERE WAS GP AND PATIENT AGREEMENT

Medication Classes	Frequency	Percent	Cumulative Percent
Usual care			
Calcium channel blocker	4	23.5	23.5
Antiplatelet	3	17.6	41.2
Diuretic	2	11.8	52.9
Anticonvulsant	1	5.9	58.8
Immune suppressant	1	5.9	64.7
Long-term antibiotic	1	5.9	70.6
NSAID	1	5.9	76.5
Opioid analgesic	1	5.9	82.4
Other	1	5.9	88.2
Supplement - multiple ingredient	1	5.9	94.1
TCA	1	5.9	100.0
Total	**17**	**100.0**	
Intervention			
Supplement - single ingredient	12	25.0	25.0
Diuretic	5	10.4	35.4
Bisphosphonates	4	8.3	43.8
Oral hypoglycaemic	4	8.3	52.1
Other	4	8.3	60.4
Anticonvulsant	2	4.2	64.6
Calcium channel blocker	2	4.2	68.8
PPI or H2 antagonist	2	4.2	72.9
SSRI/SNRI	2	4.2	77.1
Supplement - multiple ingredient	2	4.2	81.3
Antiplatelet	1	2.1	83.3
Immune suppressant	1	2.1	85.4
Inhaled beta-agonist	1	2.1	87.5
Inhaled combination product	1	2.1	89.6
Inhaled muscarinic antagonist	1	2.1	91.7
NSAID	1	2.1	93.8
Other antilipidaemic	1	2.1	95.8
Paracetamol	1	2.1	97.9
TCA	1	2.1	100.0
Total	48	100.0	

Other – zopiclone, tamsulosin, calcitriol, melatonin SR.

TABLE 7-8 REGULAR MEDICATIONS TO HAVE DOSES REDUCED FOR WHICH THERE WAS GP AND PATIENT AGREEMENT

Medication Classes	Frequency	Percent	Cumulative Percent
Usual care			
Anticonvulsant	3	37.5	37.5
AT2RB	1	12.5	50.0
Beta-blocker	1	12.5	62.5
Insulin	1	12.5	75.0
Other antihypertensive	1	12.5	87.5

PPI or H2 antagonist	1	12.5	100.0
Total	**8**	**100.0**	
Intervention			
Statin	9	27.3	27.3
PPI or H2 antagonist	7	21.2	48.5
AT2RB	3	9.1	57.6
Oral hypoglycaemic	3	9.1	66.7
Calcium channel blocker	2	6.1	72.7
Allopurinol	1	3.0	75.8
Anticoagulant	1	3.0	78.8
Antiplatelet	1	3.0	81.8
Beta-blocker	1	3.0	84.8
Insulin	1	3.0	87.9
NSAID	1	3.0	90.9
Oral corticosteroid	1	3.0	93.9
Other	1	3.0	97.0
SSRI/SNRI	1	3.0	100.0
Total	**33**	**100.0**	

Other = Norgesic

7.4.2.5 Medications that were altered through reconciliation

Step one of the application of the CEASE protocol (91) by a clinician is medication reconciliation, i.e. deleting, adding or amending doses of medications to reflect current true use. Medication reconciliation was performed 5.1 times more frequently among intervention patients compared to usual care patients (IRR 5.0, 95% CI 3.085 to 8.244, p <0.001), such that the mean difference in the number of medications reconciled between groups was -2.078 (95% CI -2.662 to -1.494, p <0.001).

7.4.3 Sensitivity analyses to account for protocol breaches

Three sensitivity analyses were performed to account for changes in study protocol. The Per Protocol analysis was specified *a priori*. The Per Protocol analysis, in contrast to the ITT principle described previously, refers to conducting the analysis based on the study participants' (in this case the patients') actual receipt of, rather than original allocation to, the intervention. The Per Protocol analysis would be comparable to the ITT analysis if there was a high level of protocol adherence in the study.

Two sensitivity analyses were not specified *a priori* because they could not be pre-empted in this exploratory study. That is, two GPs stated in their follow-up semi-structured interview that they deviated from the procedure to identify a consecutive sample of eligible patients to be contacted by the research team for recruitment (see 7.2 Adherence to protocol, for more detailed information regarding this). Furthermore, one GP left the

practice mid-study and so the analysis was repeated excluding their patients to see if this had any impact on the effect size. As demonstrated in Table 7-9, the effect size remained stable and statistically significant, regardless of the unanticipated protocol deviations.

TABLE 7-9 SENSITIVITY ANALYSES OF AGREED[A] GP AND PATIENT-REPORTED CHANGES TO REGULAR MEDICATIONS PER PATIENT DURING THE STUDY PERIOD FOR INTERVENTION AND USUAL CARE GROUPS

Outcome	Measure of central tendency	Intervention (SD) [n]	Usual Care (SD) [n]	Mean Difference[c] (95% CI)	IRR[d] (95% CI)	P value
Medications Deprescribed[b] –						
Per protocol	Mean	1.03 (1.241) [n=75]	0.41 (0.825) [n=70]	-0.612 (-0.957- -0.268)	2.461 (1.410-4.295)	0.002
	Median	1 (0-2)	0 (0-1)			
Excl. patients of two GPs who breached recruitment protocol	Mean	0.93 (1.226) [58]	0.43 (0.839) [67]	-0.498 (-0.877- -0.119)	2.223 (1.223-4.043)	0.009
	Median	0 (0-2)	0 (0-1)			
Excl. patients of GP who left the practice mid-study	Mean	1.01 (1.225) [67]	0.43 (0.839) [67]	-0.582 (-0.941- -0.223)	2.331 (1.315-4.130)	0.004
	Median	0 (0-1)	1 (0-2)			

[a] Agreed indicates agreement of the deprescribing change between the GP record and patient-report.
[b] Includes ceased and dose-reduced medications.
[c] Equal variances not assumed if p-value for Levene's Test for Equality of Variances was <0.05.
[d] IRR - Incidence Rate Ratio (adjusted for number of baseline regular medications, age and gender).

7.4.4 Intervention impact on patients' attitudes to deprescribing and quality of life

The Patients' Attitudes Towards Deprescribing (PATD) questionnaire was administered to intervention patients at baseline and follow-up. The EQ-5D-5L was administered to all patients at baseline and follow-up. See Appendix 17 and Appendix 18 for copies of each.

Pre- and post- intervention PATD responses were used to assess changes in patients' attitudes towards their medication regimens and deprescribing over the study period. Baseline scores were also used to test for an association between baseline responses and deprescribing outcomes.

The EQ-5D-5L was used to assess self-reported health-related quality of life (HRQoL) over the study period. The rationale for including this quality of life measure was as a 'red flag indicator', i.e. to indicate whether the intervention was causing short-term harm, rather than longer-term benefit, the latter typically seen over a much longer study period in regard to HRQoL. Consequently, the responses for the first five domains of the EQ-5D-5L which

use a five-point Likert scale were dichotomised to reflect an improved or worsened score in the domain. The global health score out of 100 was reported unchanged.

7.4.4.1 PATD survey responses over study period

The paired pre- and post-intervention patient response rate was high, with eight out of 10 statements on the questionnaire survey having a paired response from 73 of 75 patients, noting that three of the 78 intervention patients were lost to follow-up and did not participate in the follow-up phone interview. The PATD ten statements were scored on a five-point Likert scale: 1 = Strongly Agree; 2 = Agree; 3 = Unsure; 4 = Disagree and 5 = Strongly Disagree. There were statistically significant changes between pre- and post-intervention responses for three of the ten statements in the PATD questionnaire, as seen in Table 7-10. Two of the statements pertained to the necessity of the current medication regimen and one pertained to the belief of side effects with the current regimen.

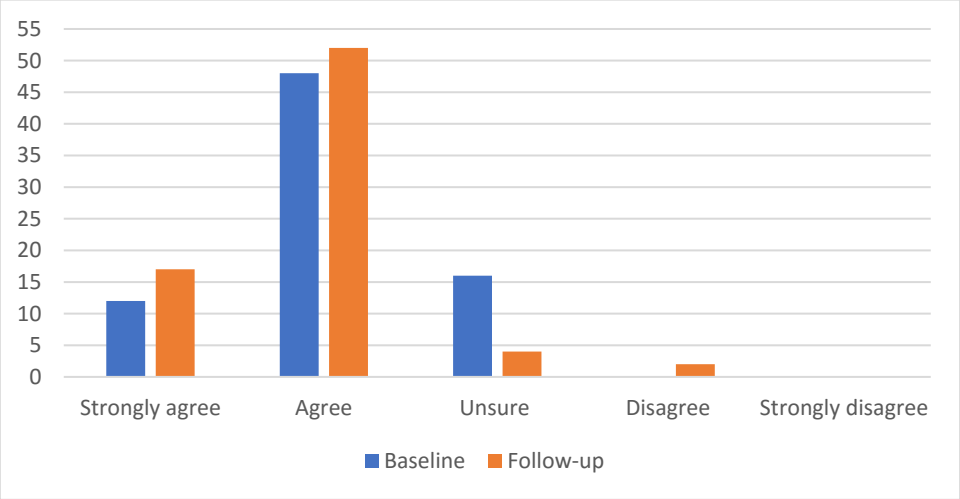
TABLE 7-10 RESULTS FOR PRE-AND POST-TEST PATD QUESTIONNAIRE RESPONSES

PATD Question (n = paired responses[a])	Mean at Baseline	Mean at Follow-up	P (2-tailed)[b]
1. I feel that I am taking a large number of medications (n = 71)	2.47	2.55	0.360
2. I am comfortable with the number of medications I am taking (n = 72)	2.36	2.27	0.386
3. I believe all my medications are necessary (n = 73)	2.05	1.88	0.013
4. If my doctor said it was possible I would be willing to stop one or more of my regular medications (n = 73)	1.79	1.91	0.287
5. I would like to reduce the number of medications that I am taking (n = 73)	2.24	2.33	0.623
6. I feel that I may be taking one or more medications that I no longer need (n = 73)	3.24	3.76	<0.001
7. I would accept taking more medications for my health conditions (n = 73)	2.36	2.33	0.509
8. I have a good understanding if the reasons I was prescribed each of my medications (n = 73)	1.83	1.75	0.524
9. Having to pay for less medications would play a role in my willingness to stop one or more of my medications (n = 73)	3.37	3.60	0.063
10. I believe one or more of my medications is giving me side effects (n = 73)	3.05	3.40	0.012

[a] Non-paired responses were excluded from the analysis. [b] Tested using Wilcoxon signed rank test

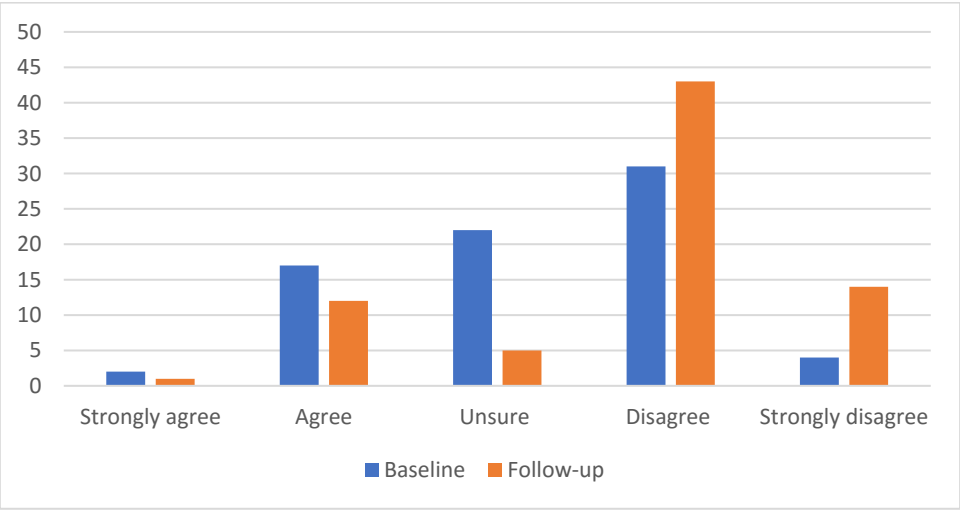
For the statement, “I believe all my medications are necessary”, the decrease in mean score post-intervention as seen in Table 7-10, reflected greater agreement with the statement ($z = -2.475$, $p = 0.013$). That is, overall, more people believed their medications were necessary after the intervention than before. Figure 7-2 shows the shift in response between baseline and follow-up. There were two and five missing responses, at baseline and follow-up, respectively.

FIGURE 7-2 FREQUENCY OF PAIRED RESPONSES TO PATD STATEMENT "I BELIEVE ALL MY MEDICATIONS ARE NECESSARY"



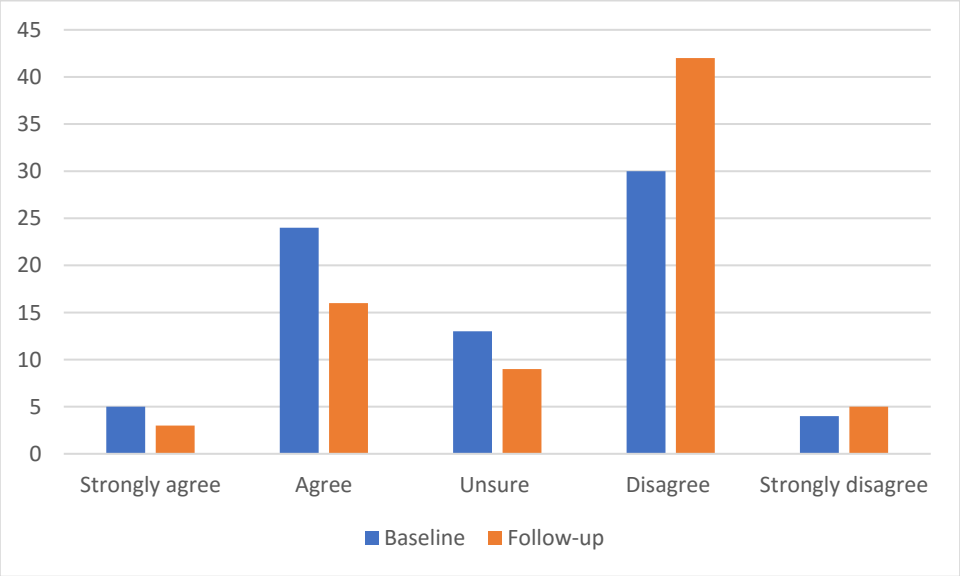
For the *negatively* worded statement, “I feel that I may be taking one or more medications that I no longer need” the increase in mean score post-intervention as seen in Table 7-10 reflected greater disagreement with the statement ($z = -4.067$, $p = <0.001$). Note that greater disagreement with a negatively worded statement is equivalent to greater agreement with a positively worded statement. That is, overall, fewer people believed their medications were unnecessary after the intervention than before. Figure 7-3 shows the shift in response between baseline and follow-up. Notably, 22 participants were unsure in response to this statement at baseline, as opposed to only five at follow-up. There were two and three missing responses, at baseline and follow-up, respectively.

FIGURE 7-3 FREQUENCY OF PAIRED RESPONSES TO PATD STATEMENT “I FEEL THAT I MAY BE TAKING ONE OR MORE MEDICATIONS THAT I NO LONGER NEED”



For the statement, “I believe one or more of my medications is giving me side effects” the increase in mean score post-intervention reflected greater disagreement (z = -2.521, p = <0.012) as seen in Table 7-10. That is, overall, fewer people believed their medications were giving them side effects after the intervention than before. Figure 7-4 provides a breakdown of responses. Notably 12 more patients disagreed with this statement at follow-up than at baseline. Again, there were two and three missing responses, at baseline and follow-up, respectively.

FIGURE 7-4 FREQUENCY OF PAIRED RESPONSES TO PATD STATEMENT “I BELIEVE ONE OR MORE OF MY MEDICATIONS IS GIVING ME SIDE EFFECTS”



The intervention appears to have shifted patients’ views about their medication regime. For example, patients who responded at baseline that they were either unsure of the necessity or appropriateness of their medication regimen or felt it was not necessary or appropriate, shifted towards greater certainty or agreement that the medication regimen was in fact necessary or appropriate.

7.4.4.2 Baseline patients’ attitude towards deprescribing as a potential predictor of medications deprescribed

As described in section 6.7.3.2.1, principal components Factor Analysis was conducted to reduce the 10 PATD statements with Likert scales into a smaller number of underlying variables that explain the pattern of correlations within the baseline PATD dataset. (211) These variables are known as ‘Factors’ and analysis generated four Factors. Appendix 19 details the output from SPSS, including the Rotated Component Matrix. All four Factors

accounted for 69.3% of the total variance. Factors 1 and 2, which accounted for 45.5% of the total variance, were retained for further analysis but the Factors 3 and 4 were discarded, with loadings for only one and two of the possible ten PATD survey items. See Appendix 17 to review the first ten items of the PATD survey.

Factor 1 had high loadings for PATD survey items 1, 4 and 5. This set of questions related to a willingness to consider deprescribing at baseline (participants felt they were taking a large number of medications, were willing to stop one or more regular medications and wanted to reduce the number of medications taken). Factor 2 had high loadings for PATD survey items 2, 3 and 6 but survey responses for item 6 were reverse coded so that all scores for this factor were positively correlated. This set of questions related to satisfaction with the medication regimen at baseline and arguably less willingness to consider deprescribing (i.e. participants were comfortable with the number of medications they were taking, believed that all their medicines were necessary and did not feel they were taking medicines that were no longer needed).

Neither Factor 1 nor 2 were statistically significant predictors of the primary outcome when imputed into the Negative binomial regression model (Factor 1 Exp(B) 0.946, 95% CI 0.636 to 1.407; p = 0.785; Factor 2 Exp(B) 1.148, 95% CI 0.781 to 1.689; p= 0.482).

7.4.4.3 Quality of life over the study period

As seen in Table 7-11 below, Chi squared tests for independence did not show a statistically significant change in responses pertaining to any of the five HRQoL domains.

TABLE 7-11 CHI-SQUARED TEST FOR PAIRED-RESPONSES TO DICHOTOMISED EQ5D5L STATEMENTS

Domain	% of Intervention patients who reported worsened score (n = 64)	% of Usual Care patients who reported worsened score (n = 73)	Continuity Correction Sig. (2-sided)
Mobility	18.8%	31.5%	0.131
Personal Care	10.9%	8.3%[a]	0.823
Usual Activities	31.3%	21.9%	0.297
Pain/Discomfort	25.0%	18.3%[b]	0.462
Anxiety/Depression	25%	11.0%	0.053

[a] n = 72 due to missing data.
[b] n = 71 due to missing data.

There were 63 and 70 paired global health score responses for intervention and usual care patients, respectively, demonstrating a response rate of 90% or more for both groups. There was no statistically significant difference in paired global health change scores (on

the 0-100-point scale) between intervention and usual care patients (mean change -1.84 for the intervention group and -1.30 for the usual care group, p = 0.842).

7.4.5 Self-reported unplanned hospitalisations

Poisson regression modelling adjusting for age, gender, number of GP-patient agreed regular medications at baseline and number of common chronic comorbidities showed a trend towards reduced numbers of self-reported unplanned hospitalisations among intervention patients compared to usual care patients during the study period, IRR 0.4, 95% CI 0.183-1.014, p = 0.054. Data were missing for four intervention and two usual care patients.

7.5 Safety protocol

7.5.1 Suspected/actual adverse outcomes or experiences

No actual adverse outcomes were reported to the research team throughout the study period. Two forms to report suspected adverse outcomes or experiences (see Appendix 3) were completed however, as a result of patient dissatisfaction with the deprescribing process. The first form was completed by the PhD candidate after being contacted by a patient directly. This patient had incorrectly attributed the emergence of a new health complaint to the reduction in dose of two medications and the patient was followed up by their GP for ongoing care. The second form was completed by one of the GPs following the patient's expression of dissatisfaction at having her medications altered. The latter incident related in part to the patient feeling that the GP making the change was not their principal GP and has been described in detail in Chapter 8.

7.6 Discussion

The results in this chapter address the effectiveness and safety of the multifaceted intervention on the medication regimens of older community based patients with polypharmacy, and patients' attitudes towards deprescribing and self-reported quality of life. The vast majority (96%) of intervention patients had an initial deprescribing appointment as scheduled. The mean difference between intervention and usual care groups in the number of regular medications deprescribed per patient was -0.55, 95%CI -0.897 to -0.212, p = 0.002. Compared to usual care patients, intervention patients were 2.3 times more likely to have one or more medications deprescribed (ceased or doses reduced) over the 18-week study period after adjusting for age, gender and the number of baseline regular medications. Crude totals showed 77 of 649 (11.9%) baseline regular

medications in the intervention group were deprescribed compared to 29 of 571 (5.1%) corresponding medications in the usual care group over the 18 week study period ($p<0.001$). There was no statistically significant change in the number of medications commenced or increased between groups over this same period. Compared to usual care patients, fewer intervention patients with hyperpolypharmacy (≥ 10 regular medications) had no medications deprescribed. The main medication classes deprescribed in intervention group patients were single ingredient supplements, proton pump inhibitors and H2 antagonists, statins, oral hypoglycaemics and diuretics. There was no statistically significant difference in the number of GP appointments, HMRs, or self-reported unplanned hospitalisations between intervention and usual care patients, noting the limitation of small event numbers for the latter two measures.

For intervention patients who, at baseline, were either unsure or disagreed with the necessity or appropriateness of their medication regimen, receiving the intervention appears to have increased their certainty or agreement that their medication regimen at follow-up was in fact necessary or appropriate. Participating in the study did not deleteriously affect self-reported HRQoL and was not associated with any reported harm.

There are three key methodological limitations to this study. A threat to the internal validity was the potential for selection bias by GPs in the generation of a consecutive sample of eligible patients for each GP. Although a clear and documented procedure was provided to each GP (or their nominated delegate) to do this, two GPs advised that they did not strictly adhere to this procedure. It is possible that other GPs, even subconsciously, may have influenced the patient selection process. The rationale for not insisting on random patient selection was to avoid the additional burden this would have imposed on GPs (or their delegate) and the desire to minimise barriers to project participation, particularly in the context of time-limited recruitment challenges. Even though sensitivity analyses showed that the size and statistical significance of the primary outcome was preserved when the patients of the two GPs who did not adhere to the procedure were excluded, it is possible that these study results may have differed had patients been selected randomly.

Likewise, the reliance on a convenience sample of practices and clinicians may have introduced sampling bias in this exploratory study. This potential bias is likely to have significantly less impact on results than that arising from patient selection bias however, as studies to change clinician behaviour typically tend to be conducted in groups of ‘early adopters’ (that is, those with interest in the topic for investigation, who are open to new

ideas and usually demonstrate a high 'readiness to change'. (217, 218) These participants are unlikely to be representative of 'typical' practices/clinicians, with significantly different characteristics. (217) It is possible, however, that these 'early adopters', with an existing interest in the topic of investigation, may have already changed their prescribing behaviour, leaving little margin for further deprescribing of inappropriate medicines, thereby reducing any positive effect size.

The absence of independent outcome assessors and reliance on data collection from medical records which clearly revealed patients' group allocation, prevented blinding of assessors/investigators, introducing the potential for ascertainment bias. (219) This was mitigated to some extent by cross-referencing data regarding changes in medications between patients and GPs in constructing 'agreed' lists of changes, and the high inter-rater reliability in the application of a standardised, documented process to categorise medication changes only from the GP record.

There were also several methodological strengths to this study. This is one of the first studies to elicit patients' attitudes towards their medicines and deprescribing at baseline using the PATD questionnaire and to investigate the relationship between baseline scores and the outcomes of deprescribing (which was not medication class specific). Although no association was found between baseline PATD responses and deprescribing outcomes, the change in PATD scores during the study provide interesting insights. It is possible that the increased belief in the necessity and appropriateness of medicines perceived by some patients, could have implications for improved adherence, although this needs to be studied further.

Other strengths relate to robust and standardised data collection processes given the pragmatic design. For example, strategies to ensure a standardised approach when collecting data from patients over the phone, included: 1) the development and use of a standardised data collection template and question guide for interviewers; and 2) ensuring, wherever possible, the same researcher conducted the baseline and follow-up survey.

Other examples included the use of strategies such as collecting data from medical records to the point of saturation (as was employed when documenting patients' chronic conditions at baseline by scrutinising GPs notes, hospital discharge letters and specialist correspondence until no new chronic conditions could be detected) and, wherever possible, cross-referencing patient-reported outcomes with the medical record to increase

the accuracy of the data. Furthermore, reporting 'agreed' medication outcomes mitigated to some extent the potential effect of patient recall bias. Although reporting the medication related outcomes in this way diminished the effect size, it was deemed to be the most robust and conservative method for presenting the data.

Some key points are noteworthy when comparing this study to other studies investigating interventions to reduce polypharmacy in community living older people. The systematic review and meta-analysis by Johansson *et al* of strategies to reduce polypharmacy on clinically relevant endpoints showed that the weighted mean number of drugs was reduced by -0.2 of a medicine in the intervention group but increased +0.2 of a medicine in controls. The mean difference in the number of medicines ceased per patient between the intervention and usual care group in this study was -0.362 (95% CI -0.652 to -0.071, p= 0.015), which is an effect size comparable to that reported by Johansson. (30) This study, being exploratory in nature, had a shorter length of follow-up compared to studies detailed in Johansson's review (four months compared to 12 months for most trials, range 1.5-18 months), so it is therefore unclear if the effect observed in this study would have been preserved or changed over time. (30) This is important to consider given findings from previous studies that as many as one quarter of medicines deprescribed are restarted within 6 to 12 months. (220, 221)

In evaluating this study, no attempt was made to assess the appropriateness of the medicines deprescribed using explicit or implicit criteria given their limitations. For example, explicit checklists (such as the Beers criteria) are typically divorced from the highly contextualised process of individualised therapeutic decision-making, required when considering deprescribing in older patients with multimorbidity and polypharmacy. Implicit criteria, such as the Medication Appropriateness Index (MAI), exhibit floor effects, such that the number of 'inappropriate' ratings tend to be low.(81) This was clearly demonstrated in a pilot study which studied the feasibility of a quality use of medicines intervention in a GP and patient cohort very similar to those studied here. (115) Muth and colleagues investigated a complex intervention which prioritised multiple medications in community living people aged 65 years and older with three or more chronic conditions and five or more chronic prescriptions across 20 general practices in Germany over 12 weeks. (115) The primary outcome was a change in the MAI at the patient level, which was not shown to be statistically significant at study completion. One of the key reasons for this was that the baseline MAI scores were very low (indicating high medication

appropriateness), leaving very little scope for a further decrease in MAI scoring. (115) The application of the MAI was also highly labour intensive and time consuming, making its application unfeasible within the time and resource constraints of this PhD research project.

Similarly, no attempt was made to assess under-dosing of appropriate medicines in this study, although it is acknowledged that this also deserves attention in older people with polypharmacy. (52-54) It is speculated however, that deprescribing may be an entry point to more appropriate prescribing and medicines use generally. That is, reducing potentially inappropriate polypharmacy may optimise patients' medication regimens and improve their adherence to essential therapy. (222) This further supports the need for greater investigation of the impact of deprescribing on patient adherence to essential therapy and whether it is the deprescribing process or outcome that is important in facilitating any potential beneficial effect.

An important unanswered question from this study regards the fulfilment of intent to deprescribe. Unfortunately, there was insufficient consistent documentation to indicate if, for example, GPs wished to deprescribe more potentially inappropriate medicines (PIMs) but patients were unwilling. This would have been interesting to elicit, given conflicting qualitative research that GPs report it is patients who are often unwilling to deprescribe PIMs, (9) yet patients report that their GP can be highly influential in encouraging them to deprescribe medicines. (8)

7.7 Conclusion

In summary, the intervention lead to a clinically modest but statistically significant deprescribing effect in community living older people. The intervention was not associated with a higher number of GP visits or referrals for HMRs (i.e. the optional component of the intervention). Importantly, the intervention was also not associated with any reported harm or deterioration in quality of life in the short-term which may have resulted from injudicious attempts at deprescribing appropriate medication. For a subset of patients, there was greater belief that their medication regimens were necessary and appropriate. In the next chapter (Chapter 8), qualitative findings will be presented to describe the feasibility of the intervention and further explain some of these quantitative findings.

Chapter 8 Qualitative findings of Phase 3 exploratory study

Complementary to Chapter 7 which reported the quantitative perspective on the intervention's effectiveness, this chapter expands on this reporting with the qualitative findings of semi-structured interviews with GPs and patients after completion of the intervention. To that end, this chapter provides insights into the implementation of the intervention in practice, including adoption of its elements, acceptability, and the likelihood of sustainability in routine care. These three constructs have been defined using the work of Proctor *et al* (144) such that: adoption is the 'intention, initial decision, or action to try or employ an innovation or evidence-based practice'; acceptability is the 'perception among implementation stakeholders that a given treatment, service, practice, or innovation is agreeable, palatable or satisfactory'; and sustainability is 'the extent to which a newly implemented treatment is maintained or institutionalised within a service setting's ongoing, stable operations'. The perspectives of GPs regarding the earlier phases of the intervention are reported first before providing an integrated GP and patient perspective on the deprescribing consultations and arising consequences. As described previously in Chapter 6, a qualitative descriptive approach was used, which has been shown to be an appropriate choice for mixed methods health services research. (142) Thematic analysis was conducted deductively initially, with responses segmented according to interview questions which aligned with the intervention phases. The second step involved developing the themes inductively, with reference to concepts from the study of feasibility literature. (215)

8.1 Findings

Findings of the analysis are organised and discussed by way of three descriptive themes: 1) *Adoption into GPs' practice;* 2) *Perceived value of deprescribing* and; and 3) *Spread and sustainability*. The first and third themes principally reflect the views of GPs as the primary adopters of the intervention. The second theme is an integrated perspective of GPs and patients as joint adopters of the intervention from the point of the deprescribing appointment/s onwards. Extracts throughout this chapter reflect both divergent and convergent views and were labelled with a unique identifier. Quotations from GPs and patients are denoted by GPxx and Ptxx, respectively, where x reflects a number from 0-9.

8.1.1 Adoption into GPs' practice

Adoption of the intervention involved the GP (or for the first activity, their practice delegate) actioning or attempting to action the three mandatory components of the intervention (that is, identifying potentially eligible patients, participating in the deprescribing workshop and having at least one, extended deprescribing appointment with each of their patients). GPs reported a range of factors that were facilitative and/or inhibitory to each of these activities.

8.1.1.1 Identifying potentially eligible patients

This element of the intervention, that is, identification of eligible patients, was to be aided by a software query. However, this was impeded by out of date medication lists and uncertainty about the patient's preferred GP. In turn, GPs compensated by using the manual screening process, which had been devised in advance in anticipating data quality issues.

> *GP04: It – it had to do the manual checking part of it as well - - -*
>
> *Int: Mmm.*
>
> *GP04: - because, um, it did – it does do things like throw – I do recall it threw up patients that weren't actually my regular patients that I'd just seen once or twice and -*
>
> *Int: Right. Yeah.*
>
> *GP04: - um, for some reason. Um, I'm sure there was some other issues with it -*
>
> *Int: Mmm.*
>
> *GP04: - the – the – so it did need that sort of manual tuning. Yeah -*

Although not perceived to be burdensome by intervention GPs, the task of identifying eligible patients clearly did take time and some GPs required prompting for this to occur in time for the deprescribing workshop. Moreover, this time had to be found often after hours, as described by this GP.

> *GP06: "Um, I don't know. I – I think it depends a little bit on your perception of what's onerous and I'm perfectly happy to sit here and I mean, I'm sure I sat here after hours and just went through the list and worked out who was who and went through it, but for me, no, it wasn't onerous."*

Similarly, regarding identifying patients for the study, one GP stated -

> *GP08: I don't think that it took any - much more time than it does to do any other quality improvement process.*
>
> *Int: Okay.*
>
> *GP08: Less than most, really.*

These comments suggest an acceptance or willingness on GPs' behalf to invest the time to identify patients to make the intervention work. A number of GPs also highlighted the benefit of this exercise, beyond the intervention. In response to being questioned about the time spent identifying patients, one GP responded -

> *GP09: I think it was a good thing for me.*
>
> *Int: Right.*
>
> *GP09: Because it really did highlight, um, out of that list then well really who am I targeting.*
>
> *Int: Yes.*
>
> *GP09: Um, so for me it was a - it was a win-win.*

One practice took this further and used the process of patient identification to flag individuals for other potential activities, like health assessments and multidisciplinary care plans.

> *GP02: But it is – it's sharpened the focus on what the doctors do with care planning.*

While the process of identifying patients required an investment of time and effort, it appeared acceptable to GPs as it was perceived a necessary first step for the intervention.

Some also found value gain in identifying a vulnerable patient group for their own awareness or other health activities despite the trade-off of time. That said, the combination of data quality issues and the requirement for prompting to facilitate this task in a timely manner raises questions about the sustainability of this aspect of the intervention.

8.1.1.2 Deprescribing training workshop

There was overwhelmingly positive feedback from all GPs regarding the training workshop. The GP participants reported that the presentation of the evidence pertaining to polypharmacy and deprescribing raised their awareness of the need for deprescribing. The practical and interactive application of elements of the CEASE framework to case studies was also highly valued.

> *GP02: The workshop was excellent, um, identifying, um, the problem and the scope of problem and some well-presented ways of managing it.*

They articulated that other practical aspects of the workshop, including how to document deprescribing interactions in their software, were also helpful in adequately preparing them for adoption of the intervention.

> *GP05: I thought it was very good, that workshop. Um, went through - it went through all the major issues that we - we were trying to address very well. It had - had a section on the practical, um, step-by-step processes and that about what we're doing and it was also adapted to the - the Best Practice system.*
>
> *Int: Yes.*
>
> *GP05: So we had that auto, ah, fill - - -*
>
> *Int: The auto fill shortcut, yeah.*
>
> *GP05: - - - which worked very well. I mean, obviously I came back and had a little go with it here as well, but it seemed to work very well. So I thought I was pretty well prepared for it.*
>
> *Int: Yes.*
>
> *GP05: And we - for - for when - when we did it.*
>
> *Int: Yeah. What - - -*

GP05: Um, I can't think of any major issues that arose doing it that we hadn't covered in the - in the, ah, workshop, yeah.

This GP's experience of the workshop, likewise for another, motivated them to present the material at a clinical practice meeting and articulate the need for deprescribing to their peers. There was agreement from other GPs that the training workshop should be made available to GP colleagues not involved in this study –

GP09: I thought it was fabulous. Um, honestly, I thought that whole day was brilliant. Um, and I'd replicate it again and highly, I suppose, recommend (it to) everyone. Not just anyone - just I suppose outside of the realm of this actual study itself of an actual workshop for educating GPs regardless -

Int: Right.

GP09: - I think it would be really valuable as well.

The face-to-face interactive workshop was therefore a key component of the intervention, providing important theoretical and practical deprescribing support. It was also perceived as being valuable and applicable to GPs not involved in the exploratory study. This was reinforced by the example of peer knowledge translation in which two GPs were motivated to share knowledge from the workshop with other colleagues in their practice.

8.1.1.3 Deprescribing appointment/s

Deprescribing appointments with patients were core to the intervention. Most GPs indicated that the intervention was more an opportunity for refinement of patients' medication regimens rather than making wholesale change, as described in this extract.

GP08: I guess you'd have to think that if you've been trying to do that, um, deprescribing, um, all along you may have not that much wriggle room left, um, in some of the steps that you wanted to take in those individuals.

They attributed this to a number of factors - either that their prescribing was appropriate to begin with and/or that deprescribing was something they had already considered, albeit largely opportunistically. Consequently, GPs perceived that their deprescribing efforts involved working at the margins, as the same GP articulated -

GP08: But my gut feeling is that I probably didn't actually achieve an awful lot of real deprescribing. Um, I – it would be at the margins, I would've thought.

Most GPs reported that the majority of work occurred at the initial deprescribing appointment. There were typically time-consuming aspects, including verifying each medicines' indication and discussions with patients about their medicines. Below, a GP explains how these issues, combined with the lack of familiarity with the application of the deprescribing process, made these appointments more time consuming initially compared to routine appointments.

> *GP10: It initially took a long time -*
>
> *Int: Right.*
>
> *GP10: - just getting heads around and patients, um, understanding exactly what we're doing -*
>
> *Int: Yes.*
>
> *GP10: - but after – once you, um – I can't even remember, um, sort of, put down, um – went through the notes and put down a reason for each medication – once you worked that out it worked quite quickly -*
>
> *Int: Okay.*
>
> *GP10: - after that it was quite quick.*

For patients in whom deprescribing was attempted for one or more medicines, subsequent visits tended to be used to monitor the effects and outcomes of changes made, rather than instigate further change.

> *GP02: I think most was achieved in this first visit, in terms of deprescribing. And some, um, I found that I wasn't really deprescribing as much at a later date, it was something that I'd reduced the dose and it was a case of moderating that adjustment.*

As described in Chapter 7, the follow-up undertaken to confirm that any changes were appropriate was not associated with an increase in the number of appointments for intervention compared to usual care patients over the study period.

For the subset of patients where GPs flagged multiple potential changes over the study period, a sustained effort over a number of appointments was required. According to one GP, in these cases structured follow-up may be a facilitator of deprescribing as it would keep the goals in mind rather than allow them to be forgotten.

GP05: Yeah. It might have been worth doing that actually, more regimented follow-up because it tends to fizzle out otherwise I think.

Int: Right.

GP05: Truthfully. I can't, you know, I think out of sight, out of mind a bit.

Int: Yes, yeah.

GP05: I think maybe after - after a few visits if you don't discuss it; it kind of -

Int: Yes.

GP05: - possibly just gets a bit forgotten.

Int: Forgotten, sure, sure. So -

GP05: And then it might have been better to have had a more formal follow-up.

Other comments indicated minor adaptations to the intervention process to better integrate it into existing workflows. Two GPs reported printing out hard copy medication lists, which were used as a tool to facilitate discussions, reconcile medication lists and create a deprescribing plan with patients, in preference to directly recording this information in the medical software in the first instance. The rationale for this change was described in terms of the power of a working partnership with the patient.

GP02: And I could do it on the screen, but I think the, the consultation, the doctor-patient experience about going through this together –

Int: Together, yes.

GP02: - is more powerful. Just looking at the screen is not going to take you off this.

Int: Of course.

GP02: Compared to (explaining to the patient) the rationale behind it.

This adaptation allowed the GPs to conduct the appointment and communicate with the patient in their preferred manner, leaving the recording of consultation notes (and the minimum documentation requirements for the research team) to the end of the interview.

8.1.1.4 Referral for HMR (optional element)

Only 10 intervention patients (13%) were referred for an HMR during the study period. The referrals came from two of three GPs at the site at which the consultant pharmacist (CP)

was co-located. Although the third GP at this same site had routinely referred for HMR, this participant ceased referrals during the study period on the mistaken belief that this was not permitted.

The consensus reasoning among the remaining GPs who did not refer patients was that it either did not occur to them, or they could not see the value in undertaking a HMR after having just done a medication review themselves.

GP07: - I don't think the - the pharmacist would offer too much more.

For some GPs this was reinforced by negative past experiences with inferior quality HMR reports, in particular the absence of relevant, individualised recommendations due to a lack, on the part of the CP, of tacit knowledge of the patient and their medical history.

The absence of an existing relationship between the trained pharmacist and GPs at the other two sites appeared to be a potential reason for non-referral. One GP explained –

GP06: Yeah and if I had any concerns I would have just popped next door (to the pharmacy)

Int: Next door. Yes.

GP06: - because I do that constantly.

The two GPs who referred patients for HMR routinely as part of the intervention, despite never engaging that pharmacist prior to the study, had mixed views on the value of this service. One GP felt that the pharmacist involvement was duplicative and unnecessary, and they did not agree with some of the pharmacists' recommendations –

GP01: No. I think it was just doubling up.

Int: It was doubling? Right.

GP01: Some of the recommendations she made, I did not agree with her.

Int: Right, yes.

GP01: If you ask me which ones, I can't (remember).

Int: No, that's okay. That's okay.

GP01: But yes, I did not agree with her and I actually left the patients on the medication. Whether it's probably because she doesn't have a medical background to – to see whether the patients need them or not (interruption – phone rang).

In contrast, another GP described the pharmacist's involvement as reassuring –

> *GP03: Yeah, I think it's a good idea -*
>
> *Int: Yeah.*
>
> *GP03: - - - to round it off and also then you get, um, well, maybe if – if somebody checking on you which is good and also it can reinforce to the patients, you know -*

Interestingly, these two GPs referred all patients recruited to the study, although some patients declined the service, rather than select the most appropriate patients for HMR.

Only four of the 10 patients who had an HMR elected to be audio-recorded. Although the feedback was limited, it was also mixed. Patients for the most part found that the pharmacist reinforced the GP's approach. For one patient for whom there were no changes to therapy, the pharmacist's home visit was perceived as duplicative to the GP's review –

> *Pt02*: Yes, I didn't think there was much value in the pharmacist coming.

Conversely, another patient appreciated the opportunity to discuss their medicines with a professional they considered to be a medicines expert –

> *Pt04: I felt good because once again you've got a specialist in a specific field that's giving you more enlightenment on the product so to speak. Doctors, yes, they do know a lot about them but it's something the pharmacist specialises in, I would think would know just that little bit more, that bit more in depth, as to some of the repercussions of taking too much of them.*

In summary, the uptake of the optional element of the intervention of HMR referral was low in the feasibility study and feedback regarding the service was mixed.

8.1.2 Acceptability

On the whole, GPs were pleased to have participated in the study, perceiving that there was an adequate return on the time invested in regard to benefits for themselves and/or their patients. A number reported that they believed the intervention had definitely changed how they practiced, although two reported that it did not. Two themes were discerned from the data obtained from GPs and patients pertaining to feasibility of changes to practice: perceived value of the deprescribing intervention; and greater satisfaction with care through consultation and collaboration in the medication review.

8.1.2.1 Perceived value of the deprescribing intervention

The majority view of both GPs and patients was that the acceptability of the intervention was not necessarily contingent on a successful trial of reducing or ceasing patients' medicines. For both GPs and patients, there was value and satisfaction in the consultation and medication review process in itself. In this example, it was the opportunity to critically reflect on the appropriateness of medication regimens.

> *GP02: Yeah, so it doesn't mean that just because you didn't change any medication you didn't get any value, no.*
>
> *Int: Right, okay, so the – there was value even – just in the process?*
>
> *GP02: Yeah.*
>
> *Int: Even if it didn't actually lead to - - -*
>
> *GP02: Yeah.*
>
> *Int: - - - an outcome? Do you – is that – am I reflecting what you've (said)?-*
>
> *GP02: Yeah.*

One GP who described the process as being beneficial for himself, went on to speculate that patients might also perceive it as better care.

> *GP05: Um, I'm sure there was some patients that didn't make any changes or else made changes and they – they reversed.*
>
> *Int: Mmm.*
>
> *GP05: Um, I guess there's some benefit to the patient in that they felt probably a little bit more cared for through the process.*

This perception was confirmed by patient reports. The perceived value of the deprescribing appointment/s was not dependent on medicines being deprescribed and that even no change to therapy could be reassuring.

> *Pt62: It just reinforced in my mind that I'm not on medications that I don't thoroughly understand or that I don't need.*

Interestingly, reassurance might also be experienced by patients where attempts to reduce therapy were unsuccessful. Here a patient, after an unsuccessful attempt to reduce a

number of medications, describes their enhanced acceptance of their regimen due to improved understanding conferred by the consultation.

> *Pt38: Yes. We talked about a lot of reasons for being on these medications. I'm still not happy to be on the medications, but I can understand why they are there. I would like to reduce them, yes, but it doesn't seem to work.*

As these two patients' comments imply, the perceived value came through a greater understanding and awareness of the need for existing medicines which patients found reassuring. This corresponds to findings in Chapter 7 that a subset of patients reported greater belief that their medication regimen was in fact necessary or appropriate after the deprescribing consultation.

The GPs also found value in the awareness raising potential of the intervention. For example, GPs described greater awareness of the potential problems of polypharmacy and a formalisation of their thinking and approach to identifying and deprescribing PIMs in their patients. One GP emphasised vigilance of patient outcomes in response to ongoing prescription of specific medicines.

> *GP02: I think it just makes you more – more alert about the long-term consequences, if you like, of some medicines you're prescribing. They are going to be (on these) for the rest of the person's life, and that should be judged on the outcomes they're producing, whatever the condition is. Are we setting up a process of monitoring to get the best outcome for the patient?*

This GP went on to articulate that, rather than simply repeating prescriptions, systematic tracking of patient progress and critical reflection on medication appropriateness should permeate thinking around prescribing.

> *GP02: And then considering at the time we prescribed, is that still on track, or do we need to change? Then to, systematically, go through - some people have been coming a long time, and just got to be in the pattern of just running out of scripts, let's just roll over the scripts.*

A number of GPs also found the process of medication review and reconciliation with their patients yielded several insights. As this GP described, there was surprise at the number of discrepancies between the medical record and what long-term regular medications patients were actually taking.

GP01: More because I think um, a lot of the patients who I thought I knew quite well and knew about their medications.

Int: Mmm, yes.

GP01: I was surprised how many were over-the-counter medications which I was not aware of.

Int: Right, okay.

GP01: So, there were quite a few. And then obviously with the deprescribings, I went through it as to what can – what is necessary and what is not necessary.

Int: Yes.

GP01: But yeah, no that – that I think was probably what – yeah, highlight – yeah, was a highlight of the thing, that I actually didn't know. Because you don't always ask patients.

For GPs and patients alike, greater awareness and understanding of the rationales for medication regimens arose from having the dedicated time and opportunity to proactively discuss and review the medicines together. This was something not routinely afforded to patients in the busyness of usual appointments, as this patient described -

Pt55: I thought it (the deprescribing appointment) was very good actually, because (usually) you go in and say what's wrong and everything and the GP will say well I think you should try this and we will see how this goes. You don't really get the time because they are only supposed to give you 15 minutes. In 15 minutes, you can't really discuss something if you had another reason for going there. So yes I did have time to discuss it and I felt it was beneficial.

As indicated, the shorter appointment times and competing clinical priorities of routine appointments generally precluded in depth discussion of less-urgent clinical issues, making the extended medication review appointment a particularly beneficial element of the intervention.

Another patient offered that the value of the intervention was in putting the issue of deprescribing on the therapeutic agenda for discussion, something that neither the GP nor patient had ever previously raised.

Pt51 – I think it is excellent that we had that chance because I can't remember it ever happening before. But I can remember, at various times, talking to friends and neighbours about medication, that a lot of us sort of scratch our head, and say well I have been on this for so many years, I can't even remember what it is for. It seemed a little bit strange to me that we never ever sat down with the doctor and discussed it or tried to find out whether we still really needed to be on these things. I welcomed the whole project.

A contrasting minority perspective was that a dedicated appointment was in fact superfluous because the dynamic of the therapeutic relationship was such that the patient normally felt comfortable to ask questions or raise issues with the GP during routine appointments. The following exchange suggests no benefit from having the additional appointment to review their medications.

Int: So it sounds like you've had a great rapport with (usual GP) then and you've, um, you've had plenty of opportunity to ask questions and discuss any concerns you might have just as part of a normal appointment with her then?

Pt49: Yes.

Int: Yep.

Pt49: Yeah she, ah, yeah she was good, good person to talk to.

Int: Right.

Pt49: You know, ah, if you had an appointment, she wasn't one of these that watched the clock.

Int: Mmm yep.

Pt49: You had a problem, you sorted it out.

Int: Right.

Pt49: Then and there.

Int: Right.

Pt49: So that's the type of person (usual GP) was.

As this theme implies, GPs and patients appreciated having the dedicated time and opportunity for proactive medication review, which delivered benefits through agenda

setting and greater mutual awareness and understanding of the medication regimen. However, an important minority GP and patient view was that such an appointment was unnecessary given the depth and normality of the doctor-patient relationship which provided ample opportunity for concerns and discussions about medicines to be raised as part of routine care.

8.1.2.2 Satisfaction through consultation and collaboration

Central to patients' satisfaction with the deprescribing process was a sense of adequate consultation and collaboration in the nature and timing of any changes to be made. Underpinning these collaborative discussions was the quality of the doctor-patient relationship.

When recruiting patients, GPs were asked to nominate individuals for whom they were considered the primary or 'usual GP', which was also confirmed with patients at the time of consenting to the study. A patient's satisfaction with their relationship with the GP was frequently related to a level of communication and consultation that fully met the patient's needs -

> *Pt26: Oh, yes. He doesn't hurry you. He listens to what you want to say. He doesn't push you out the door as soon as you've got there."*
>
> *Pt73: No, I don't know what her feelings are, we have such a good relationship and we sit and chat about my health, rather than sort of diagnose it clinically…*

An example showcasing the centrality of good rapport between patients and their doctors is detailed below. The context to the following comments was that a patient was recruited to the study under the care of a GP who she had seen many times, but whom the patient did not consider her 'usual GP'. This individual was taking long-term low-dose corticosteroids for an autoimmune condition which appeared not to have been confirmed by a specialist. The GP referred the patient to a rheumatologist and simultaneously attempted to reduce her prednisolone from 4mg to 3mg daily. The patient returned to the practice to make a complaint about this with the GP she considered to be her 'usual' GP. The following responses were provided by the patient at interview as to why she was dissatisfied with her deprescribing appointment and participation in the project.

> *Pt77: All doctors are different. I was just rather cross, even when I was telling ('new' doctor) how awful I felt, hands tingling, swollen feet and hands, she just kept on typing on computer, 'yes, 'yes', and I was getting crosser. I'm not happy with all*

these changes and I said, 'I want to stop'. Maybe I was uncomfortable. When I made the (second follow-up) appointment it was made with (original GP). And I said, 'I suppose you've heard about ('new' GP) and I?' And I said, 'Do you still think I should go to see the specialist?', and he said 'Yes'. I've known (original GP) for a very long time. My son, kids used to see him. I am more comfortable with (original GP).

In addition to the fact that the patient clearly felt she was not being seen by her 'usual GP', she also expressed sentiments about inadequate engagement and consultation and frustration that changes to medicines were made for a condition that had taken a long time to stabilise with the previous dosing of corticosteroid.

Pt77:… It took a long time to get the dosages that I'm on now stable and then to have changes to it, it threw me and I didn't like it. It took many trials experimenting… to be involved in this thing with you and the School of Medicine, it threw you. With (original GP), if I had marched into to see him, I would have said the same thing to (original GP), I would have been cross with him and said it straight. I'm pleased to be back under (original GP).

Examining this case from the perspective of both GPs provided an insight into how long-term relationships between doctor and patient may foster clinical inertia, with no recognition by either party for the need to critically reappraise long standing medications. The patient's 'usual' GP expressed their agreement with the specialist review. The longevity of the relationship between patient and 'usual GP' and perceived resistance to change on the patient's behalf meant there was little potential for a successful trial of deprescribing.

GP08: So, um, and it's really a question of who do you consider you have the principle relationship with.

Int: Yes.

GP08: And on some things, um, you know, ah, I've been, for instance saying to that - that particular patient that it would be good to review that diagnosis, because she's on some significant (medications) for it. And - - -

Int: Yes.

GP08: - - - ah, she had resisted the idea for many years.

Int: Yes, right.

GP08: Saying, "No. I don't want to do that. I'm very happy with how it's going."

Int: Going, yeah, sure.

GP08: Um, so really, um, the advice was - and I think that the study triggered some more, um, you know, what would you say, um, anxiety in her.

Int: Her, sure.

GP08: And, um, I don't think the outcome was all terrible. But, ah, it did, it did cause some consternation in the, you know, the process of reinvestigation and, um, and then change of medications and, I think that became quite a challenge for her.

This example highlights the inherent tensions when reconciling the patient-centred therapeutic agenda with a potentially conflicting medical agenda. The 'usual' GP was left trying to preserve the therapeutic relationship whilst still wishing to execute the 'new' GP's recommendation for specialist review.

In some instances, a stable and mutually satisfying relationship seemed to prevent open discussion about medication regimens. One patient, who had a good rapport with his GP, appreciated the opportunity afforded by the study to discuss medications.

Pt04: I've always had a very good rapport with her anyway but sometimes you know, you just, it's just suggested at the time (i.e. the medication) and you don't seem to question anything.

In this case, the patient also had an HMR as part of the deprescribing process, and found that the inclusion of a pharmacist, who they described as a "medicines specialist," facilitated the deprescribing process through the provision of more information -

Pt04: That (the HMR) was good as well because once again you've got a different perspective on the types of medication that you're taking so, you're more, yes, you're taking it for this thing, a little bit more depth on what it's supposed to do or why you shouldn't be taking too many of them and why you should possibly change and cut them down or whatever.

The situation described above is in direct contrast to the earlier statements of a patient who felt that their positive relationship with the GP meant that the deprescribing appointment was unnecessary, as they could bring any concerns to their GP at any time.

It could be inferred that the point of difference in the respective scenarios is the level of comfort the individual has in negotiating and shaping the therapeutic agenda with their GP.

Common to the few cases in which patients were dissatisfied with their GP appointment was a sense of inadequate engagement and discussion about their medications, as illustrated with this quote.

> *Pt30: To put it blankly, I thought it was a waste of time.*
>
> *Int: Sure.*
>
> *Pt30: I carted all my medication up there. It was just tipped out on the table. Looked at, referred to what was on my chart, on the computer, just checked it, put it back in the packet, that's it, boom, finished.*
>
> *Int:* Right, ok.
>
> *Pt30: No, no real, what can I say… No real challenge to get rid of any of the medication that I'm taking. According to the GP it was all necessary to look after my health, so that's it, there was no change, so that was it. Put it all back in the box and I walked out.*

It was interesting to note again that this patient did not speak up and state his expectations of the deprescribing appointment with the GP at that appointment. When asked what he would have liked to have happened, he explained –

> *Pt30: I really would have liked each medication that I'm taking to be spelled out, you know, so I could understand it properly. I've never been really told that, you know, what the medication does for me. It's always prescribed, if I run out, I just get another bloody script, repeat after repeat. That's it, no questions asked.*

In this instance, the patient's dissatisfaction stemmed from a longer-term lack of adequate communication, understanding and shared decision making about their health and medicines. This led to a sense of frustration and perceived lack of agency.

Similarly, a patient who described disappointment in the lack of "discussion, engagement, interaction and reflection" with her GP prior to attempting minor changes to her therapy for chronic non-cancer pain, described a very negative deprescribing experience -

> *Pt47: Let's just say the changes suggested by the doctor at the time of that interview, were of no help at all, in fact if anything they were disastrous. I have*

since, after experiencing, after a good eight weeks of ill health, particularly depression and anxiety, I did go back to another doctor because my previous doctor has left that surgery, and I am now back in a better place. My medications, we did change those and I am now back on medications that are helping me to sort of have a satisfactory engagement in life.

This suggests patients may be primed or predisposed to recall a negative response to conservative changes to therapy if they feel such changes occurred without adequate engagement in the decision-making process. It is also possible that the nature of the condition, such as its chronicity or potential to cause symptoms, negatively influenced the patients' perception of the outcome of deprescribing.

Conversely, adequate patient engagement, especially for those who demonstrated greater agency, increased an individual's confidence to attempt a change to therapy, as articulated by this patient -

Pt58: Well, it was a decision between the doctor [and me] so I was quite confident to go off them for that time but if anything cropped up, like with my knees… I told her the next time that I wanted to go back on them.

This extract also highlights the importance of strategies to mitigate the decrease in a patient's confidence that may result from a potentially adverse deprescribing outcome. Here the patient was reassured by the option of reinitiating therapy if required to treat symptom relapse. Patients were also comforted by the use of a gradual approach to deprescribing and planned follow-up and monitoring, as illustrated by this example.

Pt13: …I have been taken off the medication gradually over a period of time, he didn't just stop them all at once, it was a gradual thing. He has been checking to make sure that I don't have to go back on them and everything has been fine.

Adequate communication of the risks of persisting with therapy and a gradual approach to change were also suggested as ways to address patient resistance to deprescribing. This was as exemplified by this patient who was tipped towards attempting the withdrawal of her hormone replacement therapy, despite her conviction, prior to the deprescribing consultation, that this therapy was controlling her menopausal symptoms.

Pt71: I think it probably just um – it's in my, it um probably made me more aware of the fact that I should give up the Premarin.

Int: Right mmm. Did you have some um, um concerns or hesitations before, before that?

Pt71: I did.

Int: Right, and may I ask why that was?

Pt71: Well because while I was taking it I felt that I was not having the hot flushes and I felt well on it and I think because I felt well I was a bit reluctant to see where it would go.

Int: Sure.

Pt71: But after taking it down slowly, um I think it was beneficial.

Int: Sure, sure. So and I can um, can I get you to expand on why you now, that you feel it was beneficial coming off that now?

Pt71: Well mainly because I understand that they um, taking hormone replacement therapy can lead to heart attacks.

Int: Right.

Pt71: And there is heart history in my family, so…

As alluded to previously, contextual factors such as the types of long-term medications to be considered for deprescribing, the target conditions being treated, or specialty of prescriber were important influences on a patient's willingness to consider deprescribing. One patient described his unwillingness to consider changing his two long-standing antidepressants, but a willingness to consider a change to his proton pump inhibitor and dose reduction of his statin for primary cardiovascular prevention –

Pt60: Well it (the deprescribing appointment) was good really, we went through each tablet one at a time and he asked me if I would go off this and I said no, those, not the two antidepressants, we tried the Nexium but I was back on that the next morning, as I have reflux. The Caduet we decided to cut down to 80 and 5 to 40 and 5, now I am just waiting to have another blood test to see how they are working. That's about it.

In another example, a patient described that, when it came to any changes to their medication, they prioritised the views of the cardiologist, in preference to the GP, citing –

Pt45: 'Cause I see him (the cardiologist) every 6-12 months you know, and whatever he says, goes. He's the person who keeps me alive.

Int: Yes.

Pt45: You know, he (the cardiologist) knows a bit more than (the GP) does I think, and he (the cardiologist) knows a hell of a lot more than me, so what he says, I agree with.

Although this individual perceived their GP to be competent, their trust for the cardiologist was paramount and so the patient would always prioritise recommendations of the latter over and above those of the former, illustrating the highly influential and trumping role of specialists for some patients.

From the GP's perspective, confidence to attempt deprescribing was largely influenced by the patient's receptivity to having therapy altered and, particularly for preventive therapies, the clinical context and certainty of the evidence of benefit for deprescribing. As the following scenario suggests, GPs might be unwilling to assert a deprescribing agenda with hesitant patients for fear the efforts are futile and counter-productive, potentially threatening the doctor-patient relationship.

GP01: But she's also a patient who as soon you stop something, something's going to go wrong.

Int: Right.

GP01: Whether it's definitely wrong, or whether it's – from her perspective it's wrong.

Int: Wrong, yep.

GP01: So we discussed all of that and she just said, "Look, I'm not going to go off any of these. I'm going to take them, whether you say yes or no."

As this scenario suggests, GPs might be unwilling to assert a deprescribing agenda with hesitant patients for fear the efforts are futile and counter-productive, potentially threatening the doctor-patient relationship.

Akin to the situation for some patients, GPs also described the potential influence of specialists with whom they shared care of individual patients. Several GPs proactively engaged specialists in deprescribing, either directly by forwarding letters to them

expressing an intent to consider deprescribing, or indirectly by suggesting to the patient that they raise the issue of deprescribing at their next scheduled specialist appointment. In one instance, a GP reported ceasing a diuretic in a patient prior to their renal appointment, after which the specialist expressed their discontent with the GP. Although this GP provided overwhelmingly positive feedback regarding the intervention and their continuation of deprescribing beyond the study period, they admitted this experience would make them "gun-shy" in ceasing medications again without specialist consultation.

The other key influencing factor affecting the confidence of the GP to attempt deprescribing was the certainty of the evidence supporting deprescribing. As one GP explained -

> *GP05: …The whole deprescribing it's quite - it's obviously much easier if you've got a hard bit of evidence based, um, you know - to go on and I think there was that issue with the - with the one example of the, um, etidronates, five years, no fracture, um, and the evidence is – if it continues not so good. So that's quite - that's obviously one you could hang your hat on quite easily.*

This GP reflected the views of others who went on to explain that clearer evidence to support deprescribing, particularly for preventive therapies, would increase GP confidence to enact further changes.

This theme highlights the importance of patients' faith in their relationships with their doctors as a facilitator, or inhibitor, of discussions relating to deprescribing. Whilst largely facilitative, there were several examples in which the relationship was inhibitory to conversations or action on deprescribing, potentially for fear of undermining patient trust in the relationship. Patients' satisfaction and confidence in the deprescribing process appeared proportionate to the degree to which they felt consulted and engaged in the decision-making process with their GP. The context surrounding the deprescribing decision, including the condition being treated, specific medication involved and the opinion of specialists, were also influential in the decision to attempt deprescribing.

8.1.3 Spread and sustainability

The GPs, as the main adopters of the intervention, provided examples of how they integrated and expanded deprescribing in their practice during the study period. They also identified key barriers and enablers to sustainability of elements of the intervention in the longer term.

Several GPs reported that they had opportunistically deprescribed medicines in a much wider group of patients in their practice than those recruited into the study. One GP explained how the intervention prompted action with all patients.

> *GP10: It was helpful because I started doing it with everyone - - -*
>
> *Int: Oh, okay.*
>
> *GP10: - - - else, basically, um, all the other patients because the amount of times that they're on medications and you don't actually know why? Who started? When - - -even just assessing if they need it – it was actually helpful.*

For the subset of GPs who reported applying the principles of deprescribing or elements of CEASE to a much wider patient group, deprescribing was linked to a professional ethic of good practice.

> *GP10: It is – was a good reminder to actually practice medicine – how we should be practicing anyway.*

Time and competing priorities were identified as significant barriers to sustainability, such that, even within the four-month study period, deprescribing had already started to slip off the top-priority lists of two GPs.

> *GP07: Um, I think the difficult things with deprescribing is that, um, like everything else in medicine -*
>
> *Int: Yeah.*
>
> *GP07: - is - is after a while you probably, you know, other things, becomes on top of your radar…*

In part, this was because of the complexity of those patients in whom the need to deprescribe may be most pressing.

> *GP04: - because the issue is with the patients for whom this is most, um, beneficial, likely to be a problem – are also the very same patients who will come in with their list of 13 problems.*

As this GP implied, the competing priorities on the patients' agendas could scupper the agenda of proactive medication review. As a compromise, GPs described continuing efforts to opportunistically deprescribe in patients outside of the study, but adapted their approach to mitigate the time pressures in routine care -

GP04 "Um, to be honest, I don't usually explain the process to the patients – to the patients not in the study."

This adaptation has important implications, considering that patients found value in the collaborative decision-making process, rather than necessarily the outcome, of deprescribing.

For other GPs, who reported that the time invested in deprescribing efforts during the study period was worthwhile, there was some reluctance to continue this time-intensive process on an ongoing basis. One GP referred to the challenges of allocating time when patient load was significant.

GP01: It all depends on – yeah. It all depends, I think, on time.

Int: Yes, yep.

GP01: Yeah.

Int: Okay, sure.

GP01: You know, if I possibly cut back on patients, patient numbers. Then you're not so exhausted mentally to sort of go through all that. Um, but – because I do generally spend a bit of time with my patients too.

Int: Sure.

GP01: I find it hard to sort of worry about that – which it's – it's – I know it's all part of their, um, their health and their wellbeing. But um, sometimes you – you are pressed for time.

Interestingly, two GPs who initially described the barrier purely in terms of time subsequently divulged a lack of motivation as well. Some GPs highlighted that, in the absence of someone driving the initiative, and setting the agenda of deprescribing with the patients on an ongoing basis, the intervention would be unlikely to be sustained in a structured, proactive way. In this exchange the issue of embedding the intervention in routine practice beyond the study was highlighted.

GP04: So in a sense it was slightly artificial in that you did all that (set the agenda with patients) for us.

Int: Yes. Yeah.

GP04: You did – um, did the groundwork and so patients came in pre-prepared.

Int: Yeah.

GP04: Um, so there's – there's a bit about, um, how do you do that in general practice.

Int: Yes.

GP04: Now obviously you can just do it but, um, there's a – the next thing is how are you are time and cost effective about that - - -

Int: Yes.

GP04: - - - because it's – unless it's time and cost effective it's not going to happen.

Int: Yeah.

GP04: So there's, you know, some thinking to do about that, um, in the practice.

Other GPs confirmed the sentiment of the challenge to sustainability of the intervention in the absence of practice or system level changes. However, there was no consensus regarding the nature of such changes. One principle suggested making the practice manager responsible for conducting queries of databases as the basis for auditing in-practice polypharmacy and deprescribing efforts and then engaging the pharmacist or nurse within the practice to work collaboratively with the team to drive the deprescribing agenda in 'at-risk' patients. Another GP suggested linking deprescribing with existing Medicare services such as the 75-year-old Health Assessments, although they conceded there is already so much other clinical and administrative work to do during these assessments.

The GPs also spoke of current data quality issues as a major barrier to the sustainability of identifying eligible patients, undertaking deprescribing itself, and then expanding this on a larger scale. One GP explained the potential for data coding in consultations as an efficient way of documenting the rationale for initiating and altering medications in routine care.

GP02: I mean, part of the – that's another problem, and I think we're sort of not at a level of maturity in terms of understanding things like data quality, as an instructed code of data coding, in the case of the consultation, the reason, the main reasons for seeing the patient.

Int: Yes.

GP02: And then align the reason for prescribing.

Int: Yes.

GP02: Because I think there's still a big gap in terms of clinician – most clinicians have got it turned off because they actually don't realise that in essence.

Int: Right.

GP02: And one follows the other, like, if you've been coding reasons for visits, you don't have to keep finding the code for reason to prescribe, because it's actually already on your screen.

This and similar statements were couched in a broader discussion of the need for better communication between prescribers and other health professionals and across health sectors. The national eHealth agenda, including MyHealthRecord, was offered as a potential facilitator of this, despite the acknowledgement that it is still in its infancy.

Overall this theme shows that a number of GPs individually and opportunistically applied the principles of deprescribing to patients outside of the study (and targeted the same patients in conducting other health promotion activities such as the Medicare-funded 75-year-old Health Assessments). The GPs acknowledged that in the absence of system-level or practice-level change, such as using IT and other infrastructure to integrate deprescribing into usual care, the intervention would be unlikely to continue on an ongoing basis, in part due to the busyness of routine practice and competing clinical priorities in managing complex patients.

8.2 Discussion

The findings from semi-structured interviews on the feasibility of the intervention indicate that: the three phases of the intervention were adopted by GPs, although prompting was required to facilitate the identification of patients; the intervention was largely acceptable to GPs and patients; however, the sustainability of the intervention over the longer term seems in doubt without supportive changes at a practice- or system-level. Although the findings derive from a small convenience sample of 10 GPs and 52 out of 78 intervention patients, there are key learnings relating to the implementation of the deprescribing initiative that arose from the descriptive analysis as a whole.

From the GPs' perspective, if deprescribing in primary care is to occur in a proactive, planned and targeted manner, the identification of patients to target must be streamlined

and rendered efficient and accurate. This will require attention to data quality issues and improvements to software systems to facilitate data-driven quality improvement, issues that have been well-documented in primary care in Australia and abroad. (223, 224) In this study, to compensate for the existing data quality and software limitations, GPs were willing to spend the time to manually review a software-generated shortlist of potentially eligible patients, as they recognised this as an essential, first step to the intervention. The sustainability of such effort in the longer term seems unlikely however, given that prompting was required to encourage timely completion of this critical first step.

The process of having a dedicated deprescribing appointment with patients was in itself highly valued by GPs as it forced reflection on their decisions and practices. This was despite their believing that, in general, there was limited scope for deprescribing, particularly beyond one appointment, as minimising potentially inappropriate polypharmacy was already on their radar. The design of this exploratory study did not accommodate an assessment of prescribing quality (i.e. evaluating the indications and appropriate use of medicines) so it is plausible that, among a group of highly motivated GPs, achieving major gains in deprescribing may be unrealistic. This conclusion is supported by the findings of a pilot study conducted by Muth *et al* in 2016 in a very similar GP and patient cohort in Germany. This study found that baseline prescribing as assessed using the Medication Appropriateness Index (MAI) tended to be appropriate, limiting the capacity to further improve prescribing, although an alternative explanation may be the floor effect of the MAI which limits its ability to detect inappropriate prescribing. (115) However, literature also supports the case that self-assessment of clinical practice is not always accurate. As other studies have shown, GPs reviewing their own prescribing may not be aware of some of the examples of inappropriate prescribing until it is pointed out to them, for example through third party audit and feedback. (170-172)

The findings indicate that the nature and quality of the relationship between GP and patient can be both a barrier and a facilitator to the process of deprescribing. From both the GP and patient perspective, having a continuous, therapeutic relationship built on trust is fundamental to facilitating deprescribing and this finding is consistent with previous research. (8, 186) However, a notable and unique finding in this study where instances where a positive therapeutic relationship with GPs they trust may have disinclined some patients from asking questions about their long-term therapy. These patients appeared to have a lower degree of agency and other studies incriminate lower health literacy as a

contributing factor. (225) Part of the value of this intervention for both patients and GPs therefore was in establishing a therapeutic agenda and raising awareness about the potential for deprescribing through a dedicated opportunity to review and discuss the patients' current medication regimens and their ongoing appropriateness. Sinnott *et al*, who reported GPs' perspectives on an intervention to improve medication management for patients with multimorbidity in primary care, similarly found that GPs valued a dedicated opportunity to focus on prescribing, something not afforded to them in routine practice. (226)

Patient acceptability of the intervention appeared linked to the degree of consultation and collaboration with the GP in the deprescribing process, rather than the outcome, positive or negative, of deprescribing. This, combined with reassuring strategies like planned follow-up and close monitoring, could potentially overcome initial patient resistance to attempting withdrawal of some medicines. However, a range of contextual factors such as the condition for treatment, medication and specialty of the original prescriber are also influential. To date, these findings and those from other studies (9, 186) appear to indicate that, in the face of perceived patient negativity towards changes in medications, the GP will default to persisting with the status quo, until a clinical situation or trigger arises which, reactively, lends to a strong indication for an attempt at deprescribing.

The findings in this chapter also indicate that practice level and/or systems change will be required to embed and sustain proactive, planned deprescribing in routine practice in primary care. Of particular note was the GP who reported that their focus had already started to shift away from deprescribing within the study period. Whilst the phenomenon of 'provider drift' (i.e. a decay in effort/skill over time) is well established in behaviour change research, it was not anticipated that such an effect would be observed within the relatively short study period. (227) The inference is that scheduled follow-up or reinforcement activities may be required to mitigate this drift even in the short-term. Furthermore, it appears that the intervention is unlikely to become routine practice without a local champion at the practice level, assuming the role akin to the researcher in this exploratory study. As identified by some GP participants, the prompting to identify patients in a timely manner and liaison with practice staff to ensure deprescribing appointments had been scheduled on time is likely to have contributed to the high level of implementation of the intervention. Studies of other primary care change efforts have similarly found that, without an organisational change agent to drive such initiatives on an ongoing basis,

change is unlikely to be sustained into the future. (228) Other identified system barriers to sustainable deprescribing, such as poor data quality and limited inter-professional communication across different health sectors, were far reaching and not easily changed.

Finally, in identifying the core elements of this intervention which made it feasible, it appears that all three mandatory components (identification of patients through a customisable software query teamed with a manual review process, participating in the deprescribing workshop and having at least one dedicated, extended appointment with patients to review medication regimens) were essential to the adoption and acceptability of the intervention. Based on the limited data available due to poor uptake, there appeared little value in blanket referral of all patients for HMR to a CP trained in deprescribing. There may, however, be value in selected referral of patients wanting additional opportunity to discuss their medicines with a CP. There is an interesting lesson in the feedback of one GP who enthusiastically applied deprescribing principles in patients not enrolled in the study, but did so at the expense of engaging the patient in discussion and the decision making to save time. Such an adaptation accommodated the GPs' desire to deprescribe in the absence of a dedicated appointment to do so, but overlooked the fact that patients found the collaborative decision-making process more valuable than the deprescribing outcome itself. This demonstrates the importance of communicating to GPs the elements of the intervention that patients find valuable.

8.3 Conclusion

Whilst the three phases of the intervention were adopted by GPs within the study period and the deprescribing appointments and process proved valuable for the majority of patients and GPs, there are doubts regarding the sustainability of this intervention over the longer term in the absence of accompanying practice- and/or system-level changes. A more important question, is whether such an intervention should be implemented and sustained in more practices and this will only be answered once the long-term safety and efficacy of such an intervention is confirmed in a large-scale, longer-term cluster RCT. These and other important unanswered questions are discussed in the next chapter along with a discussion and synthesis of all investigations conducted as a whole.

Chapter 9 Discussion, synthesis, implications and future research

In this chapter, the findings of all investigations conducted to date as a whole are synthesised and interpreted. A summary of principal findings arising from each of the study phases are presented, followed by key learnings which are discussed in the context of relevant literature. Finally, the key strengths and limitations of the research design as well as the implications for practice and policy and future research directions are discussed.

9.1 Summary of principal findings

The overarching study aim was to develop and pilot a multifaceted GP-led intervention to minimise potentially inappropriate polypharmacy in community living older people, addressing GP and CP barriers and enablers to deprescribing in routine care. This was supported by three specific aims, which aligned to three sequential study phases, the design of which was informed by the UK MRC guidance for complex health interventions. The first two phases were developmental and used to inform elements of the complex intervention which was piloted in a mixed methods exploratory study in Phase 3.

In Phase 1, the aim was to investigate prescribers' perspectives on factors which shape their behaviour towards continuing or discontinuing PIMs in adults. A broad review of the literature, not restricted to type of prescriber or age of adult patient, was conducted to thoroughly examine all possible literature available on the topic. Most studies included in the systematic review however, explored GPs' perspectives on managing older, community living adults, which aligned with the care setting and patient group of interest for further investigation. Analysis yielded four themes pertaining to prescriber barriers and enablers to minimising the prevalence of chronically prescribed PIMs in adults: problem awareness; inertia secondary to lower perceived value proposition for ceasing versus continuing PIMs; self-efficacy regarding personal ability to alter prescribing; and feasibility of altering prescribing in routine care environments given constraints external to the prescriber. This thematic framework contributed to new knowledge by providing a way to conceptualise and understand factors which shape prescribers' behaviour towards continuing or discontinuing PIMs in adults. The analysis showed factors are complex, highly interdependent and influenced by clinical context. The analysis did not however, provide detail of the relative contribution or importance of each of these factors (that is, there were no clear 'trumping' or 'dominant' factors) and did not focus exclusively on

potentially inappropriate polypharmacy or factors specific to the Australian primary care context.

These unanswered questions justified undertaking the next developmental phase, given the overarching purpose of this study. In Phase 2, the aim was to explore the views of a sample of GPs and CPs about potentially inappropriate polypharmacy and the reasoning they apply to deprescribing in older people in primary care, including factors that influence this process. The CPs were included as they had been identified as potential change agents in primary care in Australia. The analysis of focus group discussions provided a higher degree of granularity in regard to GP and CP beliefs, attitudes and behaviour regarding deprescribing and the critical contingencies for action. Two major themes were derived from the analysis: (1) *Working through uncertainty*; and (2) *Perceived risk as a frame of reference*. *Working through uncertainty* encapsulated the immense complexity clinicians face when assessing an older person with potentially inappropriate polypharmacy, such that weighing harm against benefit in absolute terms at the level of the individual was perceived as unfeasible in most instances. However, strategies and circumstances were identified that could mitigate this uncertainty (such as targeting medicines which are easier and less harmful to deprescribe in the first instance, adopting a gradual approach to changing medicine regimens, and deferring to patients in making a deprescribing decision). *Perceived risk as a frame of reference* referred to the dichotomised view that deprescribing was a risk to be avoided or a risk to be reconciled, with tipping points in risk perception identified which might trigger action towards deprescribing.

Analysis identified critical contingencies for deprescribing, particularly the need for a continuous therapeutic relationship between the GP and patient built on trust. Furthermore, deprescribing appears largely reactive in routine practice in response to clear clinical triggers to change, namely an event signalling a change in clinical status (such as a fall that was potentially medicine-induced), or the finding of ‘low-hanging fruit’ (i.e. medications commonly cited as being overused in the medical press). Findings also suggested that risk reframing (towards deprescribing as a ‘risk to be reconciled’) and dedicated time to proactively review therapy may promote deprescribing. These learnings informed the design and components of the multifaceted intervention. Combining knowledge of behaviour change interventions that are likely to be effective with learnings from Phases 1 and 2, the three mandatory elements of the multifaceted intervention

comprised: 1) the identification of older patients with polypharmacy (to flag suitable potential candidates for deprescribing); 2) the face-to-face deprescribing training workshop (to raise awareness and reframe risks of potentially inappropriate polypharmacy, overcome prescriber inertia and increase self-efficacy to deprescribe); and 3) the deprescribing appointment between GPs and patients (to create a dedicated opportunity for proactive medication review). To overcome additional feasibility barriers for GPs such limited time, patients could be referred for an HMR to a CP who attended the deprescribing training workshop and had full access to the medical record should the GP wish.

The aim of Phase 3 was to evaluate the feasibility, effectiveness and safety of the multifaceted GP-led intervention in community living older people in primary care. The intervention was well adopted although prompting was required to facilitate timely completion of eligible patient identification and scheduling initial deprescribing appointments in some instances. The intervention lead to a modest change in medicines deprescribed which proved safe in the short-term, but, in the absence of system- or practice- level changes, it was unclear whether this effect would be sustained over the longer-term. It was also unclear if the observed reduction or cessation of regular medications, and their effects on patients' well-being, would translate to 'clinically important' outcomes over the longer-term. Medicines most frequently deprescribed tended to be supplements and classes of medications, especially preventive medications, commonly reported in the literature as being potentially overused.

Notably, a subset of patients reported greater certainty in the necessity and appropriateness of their medicines after the deprescribing intervention. This finding was consistent with qualitative data from patients who appreciated the opportunity to discuss their medicines with their GP and increase their understanding of the necessity of therapy. It also raises questions as to whether this intervention might improve adherence to essential and appropriate medicines. Baseline PATD scores were not shown to be predictive of deprescribing outcomes. This lead to speculation as to whether this instrument is too blunt to predict a change when the effect size is so small or, whether patients will follow their GPs' lead on deprescribing, as reported in the findings of a systematic review by Reeve *et al*. (8) The intervention was not associated with a deterioration in quality of life in the short-term, which would be expected as a consequence of imprudent deprescribing attempts.

The majority of GPs and patients found value in having a dedicated opportunity to proactively review medicines and in 'formal agenda setting', which is not afforded in routine practice. This was identified as a barrier to deprescribing for GPs in the Phase 2 qualitative investigation.

Despite the centrality of a continuous relationship between the GP and patient as a critical contingency to deprescribing, a long-term relationship may have precluded some patients from raising the issue of medication appropriateness with their GP previously. Patient satisfaction with the intervention was not necessarily linked to the deprescribing outcome, but rather the degree of consultation and collaboration, consistent with their needs and expectations, throughout the process. There was very little uptake of referral to CPs for HMR during the study period. Referrals which did occur were 'blanket referrals', rather than referrals based on assessments about which patients would benefit from a comprehensive medication review with a pharmacist. This lead to a sense of duplicative effort and patients feeling over-serviced in some instances.

The exploratory study was a 'bottom-up' design of a GP-led deprescribing intervention tailored for the Australian primary care context. In comparison with published literature to date, the intervention was unique in that it: 1) encouraged proactive deprescribing using structured guidance; 2) leveraged the existing relationship between implementers (i.e. the GPs) and patients; and 3) used individually-tailored versus systems-based or drug-specific approaches to deprescribing. The findings indicate that the intervention is feasible, modestly effective in facilitating deprescribing and appears safe in the short-term. The GPs and patients perceived that there was an adequate return on investment for the time and effort involved in the deprescribing intervention, more as a result of satisfaction with the process of review and reflection, rather than as a result of medications actually being ceased or having doses reduced. The long-term safety and effectiveness of this intervention, including reinforcing activities to ensure a sustained effect over time, requires evaluation in a large-scale, longer term cluster randomised controlled trial (RCT).

9.2 Key learnings in the context of existing literature

Taken together, the findings of this study as a whole indicate that deprescribing is an inherently uncertain venture and clinicians tend to react in response to a clear clinical trigger or, if deprescribing is pursued proactively, they tend to prioritise 'low hanging fruit'. In this case, 'low hanging fruit' refers to medicines for which decisions to discontinue were endowed with greater certainty, for example, medicines perceived to be overused, whose

cessation is unlikely to be resisted by patients, or where a favourable outcome of withdrawal seems more predictable. (186) As acknowledged by GPs and CPs in the Phase 2 focus group findings, this approach delivers early wins though not necessarily the best benefit as it sidesteps drugs with potential to do more harm, such as anticoagulant and psychotropic agents and opioid analgesics.(186)

Given clinicians' tendency towards 'reactive deprescribing' and an imperative in health research to demonstrate maximum 'return on investment' with finite resources, (229) there may be greater value in offering the deprescribing intervention at a time of clear clinical deterioration for a patient. This approach is advocated by Garfinkel in a study commonly cited to support the effectiveness and safety of deprescribing (the paper is discussed in detail section 2.3.4.1, 'Good Palliative-Geriatric Practice (GPGP) Guide'). (102) Despite several methodological limitations, this Garfinkel study found a mean reduction of 4.4 medications per person, significant improvement in quality of life and no significant adverse effects due to medication discontinuation. (102) There are a multitude of reasons which could contribute to the much larger effect size observed Garfinkel's study, including lack of a control group, 19-month compared to four-month follow-up, slightly older and potentially sicker patient group and the involvement of a geriatrician to identify medicines for discontinuation. Another interesting aspect of the study, however, was the timing of the solicited review in response to an identified change in the patient's care trajectory. That is, in Garfinkel's study, the patient's GP or family member referred the member to an outpatient geriatric clinic for comprehensive assessment, presumably in response to some degree of clinical or functional deterioration. At the clinic, the geriatrician then applied a deprescribing decision guide as part of the review and wrote a letter to the patient's GP recommending medications to be deprescribed, after counselling the patient/family member on the potential changes. This raises the question as to whether a larger effect size (and return on investment) could be seen if the deprescribing intervention was timed to respond to a change in the patient's care trajectory, as identified by the patient's GP, family member or patient themselves, rather than undertaken pre-emptively in the absence of a clinical cue to do so. Further research is required to establish if coupling the timing of an intervention with a perceived deterioration in clinical or functional status is a more important trigger for deprescribing than a poor clinical or functional prognosis by itself. This is supported to some extent by the findings of a systematic review which highlighted

high rates of continued inappropriate prescribing of primary and secondary preventive medicines in palliative cancer patients. (230)

If deprescribing is to be pursued in a proactive, planned and targeted manner, this investigation suggests there are two key factors that must be considered: 1) risk reframing to engender tension and appetite for change in clinicians; and 2) efficient identification of potentially eligible patients for deprescribing. As reported in the qualitative study in Phase 2, risk reframing — that deprescribing is a risk to be reconciled, not avoided due to fear of unknown/harm from deprescribing — will require high-quality research evidence of the long-term safety and efficacy of deprescribing in older people at risk of medication misadventure. Most deprescribing studies to date have been conducted in the hospital or residential aged care setting (30, 31), but well-designed and conducted, large-scale research studies supporting deprescribing will be especially important in community living older people, where loss of independence and institutionalisation could ensue following an adverse event consequent to a deprescribing intervention. The availability of such high-quality evidence may assist to alleviate clinicians' fears of the potential negative consequences of deprescribing. As shown in the Phase 1 systematic review, fear appears linked to a state of inertia resulting from omission bias (9) – the situation in which individuals deem harm resulting from an act of commission, in this case deprescribing, to be worse than harm resulting from an act of omission, in this case persisting with the status quo. (175, 176)

The identification of potentially eligible candidates for deprescribing must be streamlined and efficient to optimise uptake and sustainability. In this exploratory study, the lack of accurate, up-to-date and reliable data hindered clinicians in easily identifying suitable candidates for deprescribing based on the eligibility criteria and in quickly identifying when and why regular medicines were first initiated and by whom. This meant that GPs had to invest additional effort and time (e.g. manual screening of software-generated patient lists and time spent going through past medical records) to identify this information. Whilst GPs reported that the investment of their time and effort to compensate for the data quality issues was reasonable in this time limited study, it is likely incomplete and poor-quality data would be an insurmountable barrier to sustained deprescribing efforts for many GPs, without changes at a practice-level.

Related to the issue of identifying suitable candidates for deprescribing through use of accurate and reliable data, more research is also required to determine how drug specific

and generic approaches to deprescribing can best be coupled. As detailed in Chapter 2, many deprescribing studies targeting GPs caring for community living older people have investigated the effects of interventions on one or more specifically identified PIMs. In contrast, this study involved the application of a structured guide to support nuanced, individualised deprescribing decisions, which could apply to any medicine in any patient based on their unique clinical context. There are both positive and negative aspects to both approaches. Whilst drug-specific approaches can risk compartmentalising patients as 'users' of medicines which are assumed to be inappropriate, this approach does provide clear cues for review. Measuring the effectiveness of this type of intervention is also more straightforward and may be particularly advantageous from a public health perspective when the target medicines for deprescribing are informed by population-level prescribing data, as has been used in several studies. (113, 114) By comparison, a generic deprescribing approach relies to a greater degree on the individual clinician applying his or her discretion to review and identify (usually) their own prescribing as being potentially unnecessary or inappropriate. Finding a metric to evaluate the effectiveness of the intervention is also more challenging. The combination of data-driven drug-specific approaches to flag high-risk candidates in which a generic approach to deprescribing is subsequently applied warrants further investigation.

General practitioners as central coordinators of continuous health care are well placed to facilitate deprescribing in complex, community living older people with multimorbidity and polypharmacy. A GP-led intervention, as used in this exploratory study, allows the existing relationship with patients to be leveraged, to maximise the chance for decisions to be informed by the patient's preferences, goals and needs — elicited either implicitly or explicitly. However, given the finding in this study that patients' and GPs' perceptions of value from the deprescribing intervention did not necessarily align, further investigation of the role of formally eliciting patient preferences and goals of care to inform deprescribing is needed. This has been evaluated in other fields of research. For example, Denig *et al* published the results of a pragmatic RCT in primary care in the Netherlands which assessed the effects of a patient-oriented decision aid for prioritising treatment goals in patients with diabetes on patient empowerment and treatment decisions. (231) Although the tool was simple and easy to apply, the study findings were limited by relatively poor uptake of use of the decision aid by GPs. This may have contributed to the finding that the patient-oriented treatment decision aid did not improve patient empowerment nor clinical

parameters, over and above usual care. The authors conceded that a single exposure to such an intervention is unlikely to change patient empowerment and that instead, the use of decision aids to inform treatment decisions in patients with chronic disease should ideally be repeated and revisited over time, with greater exposure increasing the likelihood of a positive effect. (231) Incorporating specific treatment aids into a generic approach to deprescribing may be difficult, but given the potential for preference-setting to promote greater patient agency, there is merit in investigating the role of decision aids to support shared decision making and goal setting in future. Shared decision making is particularly important when evidence does not strongly support one clearly superior option or where a preference-sensitive decision is involved, as is so often the case with deprescribing in complex older patients with multimorbidity. (232) The qualitative evaluation of patients' perception of value clearly supports this as an area for further research.

From an awareness perspective, GPs may not be best placed to review their own prescribing. It may not be until a third party points out that a medicine is potentially inappropriate that the usual prescriber may be cognisant of this. (9) In this exploratory study, the involvement of a third party (i.e. medical specialist or referral to a consultant pharmacist for review) was at the discretion of the GP. Whilst some GPs did refer patients to medical specialists for review, this was not formally evaluated, and so it remains unclear if there was a higher referral rate to medical specialists in the intervention arm for input on the appropriateness of patients' current medicines. It was clear however that there was no difference between intervention and usual care patients in their referral to CPs trained in deprescribing for comprehensive medication review. One approach worthy of future investigation is the role of GP peer-review. This technique has been shown to be a feasible and acceptable approach to supporting comprehensive medication review for complex patients with multimorbidity and polypharmacy. (226) It could also be easily incorporated into the existing intervention, should it be upscaled to a larger, cluster RCT in the form of peer-to-peer review and support in existing groups of GPs within practices, after the initial deprescribing training workshop. This may also function as a reinforcing activity to minimise prescriber drift and promote the sustainability of the intervention. A recent overview of strategies to promote health professional behaviour change has shown that the most effective interventions are those which emphasise coherence, collective action and reflexive monitoring. (233) That is, for participants the work of interventions must make sense and their actual responses (collective action) must align with

expectations of external observers (reflexive monitoring). Incorporating peer-to-peer review and feedback as an element of a sustained intervention may optimise this, without increasing the burden of participation.

Finally, consistent with evidence to date, the experience from this study reinforces that facilitating any type of practice change in primary care is difficult, but designing an intervention which addresses locally identified barriers supports the change process. (40) The exploratory study showed that all three mandatory elements of the intervention were required to achieve the deprescribing effect in the short-term, but it appears that system- and or practice-level changes (which are described in more detail below) would likely be required to see a sustained effect into the future. Despite thinking that referral for HMR could overcome some of the feasibility issues for GPs such as limited time, this was not well adopted in the intervention, and could be altered for a future, larger-scale, longer-term RCT.

9.3 Implications/recommendations for practice and policy

There are clear lessons and implications for practice and policy to be taken from this study as a whole. From a practice perspective, there is an imperative for improved data quality to ensure accurate and up-to-date medical histories and current medication lists for patients to facilitate deprescribing. The need for a central, online patient health record that can be shared by health providers across multiple sectors is well recognised and a major driver of the current national eHealth agenda in which general practices have been incentivised to facilitate patient uptake of the 'My Health Record'. (234) In addition to improvements to IT infrastructure, it is clear that behaviour change on the part of health professionals and patients will be required so health information is firstly entered, and secondly, regularly curated in an electronic health record. (235) Once realised, computer-based technology may facilitate data-driven quality prescribing improvements, including for example, automatic flagging of patients who could be candidates for deprescribing, by medication load or high-risk medications.

The perspectives of GPs in the intervention study highlighted the important role of the researcher in firmly setting deprescribing on their and their patients' agenda. Local champions or change agents are likely to be key to drive deprescribing, and other quality prescribing improvements, in primary care in future. It is possible that, with the current policy context in Australia for the greater role of pharmacists within general practice, these

professionals could act as local champions to drive deprescribing and other quality prescribing initiatives, informed by local prescribing data.

There is also a greater need to encourage patient advocacy, literacy, empowerment and involvement in regard to deprescribing. This was highlighted by qualitative findings that patients largely welcomed this project. Notably, patients with strong therapeutic relationships with GPs often expressed a lack of agency to question their GP about the appropriateness and necessity of their medication regimen, even if it had occurred to them to do so. This was compounded by practical barriers of getting the issue of proactive medication review onto the therapeutic agenda, largely because of competing acute, clinical priorities.

Professional organisations and colleges have an important role in encouraging the necessary cultural and attitudinal shifts towards ‘less can be more’ in appropriate patients. The push for guideline adherence and intensification of therapy needs to be counterbalanced by the view that judicious reduction, discontinuation or non-initiation of medication, in the context of shared decision making and agreed care goals, is an affirmation of highest quality, individualised care. (63) Risk reframing, highlighting the uncertainty and harms of potentially inappropriate polypharmacy in older people is an important step to support judicious prescribing and medicines use. Raising awareness of specific cognitive biases (such as commission or regret bias arising from ill-fated action) that may inhibit clinicians from adopting deprescribing strategies will need to be part of this risk reframing process (198).

From a policy perspective, embedding and incorporating deprescribing into the curriculum for health professionals and students will be a crucial step to normalising and routinising deprescribing into medical culture and practice. This was supported by GPs clearly seeing value in the deprescribing training workshop beyond the study and being applicable to a much wider general practice audience. Central to the deprescribing training workshop was application of CEASE principals to case studies. Whilst GPs reported value in working through this decision framework for educational purposes, CEASE was not perceived as being particularly useful or applicable to support point-of-care decision making on the part of experienced clinicians. Therefore, more research investigating optimal, point-of-care decision support is required.

Finally, given the fundamental role of the therapeutic relationship between the GP and patient as the starting point for deprescribing, consideration should be given to implementing a system where patients nominate their preferred GP. This recommendation occurs in the broader policy context in Australia in which there is support for patients with chronic and complex conditions to enrol with practices under new care models, such as the Health Care Home, for the provision of coordinated, comprehensive care. (236) In the US and UK, patient empanelment or registration, in which patients are linked to one primary care physician, have been critical to facilitating improvements in primary care. (224)

9.4 Strengths and limitations

There were several strengths to this investigation, including the use of the UK MRC framework to inform the study design. The guidance provided a clear structure for the development, feasibility testing and preliminary mixed methods evaluation of the multifaceted intervention. Specifically, identifying clinicians' barriers and enablers to deprescribing in the Australian primary care context to inform the elements of the intervention are likely to have contributed to the high rate of adoption of the intervention. This is supported by the work of Greenhalgh *et al*, who has highlighted that, when implementing innovations in health service delivery, there is empirical evidence as well as robust theoretical arguments for strong linkages at the developmental stage between researchers and end-users of an innovation. (237) An innovation is more likely to be widely and successfully adopted if the researchers, when designing the innovation, collaborate closely with front-line clinicians for whom it is intended. This has also been described as co-design or co-creation, i.e. the process whereby researchers and stakeholders both contribute to the ideation, planning, implementation and evaluation of new services as a means for greater translation of research findings into clinical practice. (229, 238) Several specific elements of the intervention were co-designed throughout the study, which has been described in detail in a related publication. (239) The process of co-design may have assisted in ensuring fidelity of the intervention, whilst allowing adaptation to the local context which is characteristic of interventions that have been successfully implemented and routinised. (237) For example, working closely with practice principals or their delegates, the software query used to identify a consecutive sample of potentially eligible patients for the study was designed to be customisable according to the level of baseline data quality and capture at each site. Another example of co-design

included the refinement of the template for use in the GPs' medical software to capture deprescribing consultation notes, which also functioned as part of the data collection tool and a memory prompt for GPs at the point of care. The template was refined during an interactive session at the deprescribing workshop based on invited feedback.

The mixed methods evaluation of the intervention was a clear study strength and helped to explain how the intervention was adopted in practice, its acceptability and value to both GPs and patients, and key issues pertaining to the spread and sustainability of the intervention. In evaluating the acceptability of the intervention, the value (i.e. what mattered) to patients was identified. This is rarely evaluated in studies and is critically important if the needs and priorities of patients in regard to deprescribing are to be understood and high-value, patient-centred care is to be realised. (240) It is clear that, whilst patients found value in the process of this study, further research is needed to elicit *outcomes* that matter to patients, so that care can be designed and organised in a way that improves these outcomes. (240)

The pragmatic approach to reporting agreed medication lists and changes was innovative and maximised the validity of findings, although it potentially reduced the effect size of the intervention. It also minimised the data collection burden by GPs which is likely to have contributed to the high rate of adoption of the intervention. It did however result in greater effort for the researchers to collate and clean data, which would have to be taken into account were this intervention to be tested in a subsequent RCT.

A key limitation of the investigation was the use of convenience samples of motivated clinicians and practices. This is not unusual in studies to change clinician behaviour, which typically involve groups of 'early adopters', i.e. those with interest in the topic for investigation, who are open to new ideas, and usually demonstrate a high 'readiness to change'. (217, 218) This sampling bias potentially limits the generalisability of findings to 'typical' clinicians and practices, with two possible consequences. It could overestimate the effect size of the intervention because those sceptical of, or highly resistant to, change may be unlikely to adopt the intervention in the first place. (218) Alternatively, assuming the intervention is adopted, the size of the effect could be substantially larger in 'typical' practices or clinicians, in whom there is more scope for behaviour change and improvement. In this instance, it is speculated that the latter may be more relevant, as motivated clinicians recruited to this study, with greater problem awareness, may have

already acted to minimise potentially inappropriate polypharmacy, leaving little margin for further deprescribing, thereby reducing any positive effect size.

A final and related point to note for any future study was that practice and GP recruitment proved very challenging. This was despite incentivisation with RACGP-recognised continuing professional development and quality improvement points and nominal reimbursement for time to attend the deprescribing training workshop and identify eligible patients for the study. Difficulty in recruiting GPs into studies is not uncommon in primary care research, and a potential reason why many studies that are done in this setting are conducted in groups of 'early adopters'. (241) In a future study, however, greater effort to engage professional groups such as RACGP, in addition to the Primary Health Networks, may assist in facilitating GP and practice recruitment in this type of research.

9.5 Future research directions

In conducting and reporting the findings of this study, the following questions remain unanswered. Consequently, they are suggested as possible directions for further research:

- What are the goals and expectations of patients regarding deprescribing? Given research that patients report their GP can be highly influential in encouraging them to discontinue therapy (8), this thesis aimed to change GPs' behaviour as an entry point to facilitate deprescribing with their patients. However, patient goals and expectations of deprescribing are an unstudied and critical area of research in designing future behaviour change interventions in this field.
- How should 'deprescribing success' be defined? Clearly better metrics are needed to evaluate prescribing quality and outcomes, especially when generic approaches to deprescribing (i.e. those not targeting a particular condition or one or more therapeutic classes of PIMs) are employed. This question is particularly important in light of findings from this investigation showing that the goals and outcomes valued by health care professionals and organisations and by patients do not always align.
- How can patients be selected so that deprescribing is better targeted to those most likely to benefit, ensuring more judicious use of limited time and resources? In other words, who is most at risk and likely to benefit from a deprescribing intervention? In this study, the number of medications was used as a crude proxy of potential medication inappropriateness but reliable, predictive models for identifying individuals at risk of harm are needed. What is the possible role of combining systems-based approaches to flag suitable candidates for deprescribing (such as electronic reports driven by population-level prescribing data) with patient-level approaches supporting GPs to make nuanced, individualised treatment decisions with patients and how could this be best evaluated?

- Given the recruitment challenges, is there a demand for deprescribing interventions in primary care? How can motivation for change be best engendered to overcome deprescribing inertia? (237) Better evidence is needed to demonstrate the safety and efficacy of deprescribing but this will not be realised without primary care clinicians and practices agreeing to participate in this type of research.
- How can patients be better engaged in decision-making throughout the deprescribing process? What role, if any, do patient oriented decision aids have in formally eliciting patients care goals and preferences with regard to treatment decisions and how could this influence patient satisfaction with the deprescribing process?
- What impact, if any, does reducing potentially inappropriate polypharmacy have on patients' adherence to essential therapy?
- Are GPs best placed to lead deprescribing interventions and moderate their own prescribing? On the one hand, the existence of a positive therapeutic relationship between GPs and their patients appears largely facilitative (although there were exceptions to this). On the other hand, GPs may not necessarily be aware of their own potentially inappropriate prescribing.
- What role, if any, could pharmacists or other members of the primary care team play in future? Could practice-based pharmacists act as local deprescribing champions, systematising the identification of patients and supporting the medication review process?
- And most importantly - What is the long-term safety and efficacy of such deprescribing interventions in primary care? This will only be known if large-scale, longer-term, high quality RCTs are conducted in the primary care setting, but this will require means for dealing with the methodological and operational challenges that have been highlighted by the findings of this exploratory study (and others)

Many of the questions raised by this thesis are common to studies of other complex, proactive interventions which aim to improve health outcomes in community-living older people in developed countries (242, 243): which outcomes deliver most benefit to patients, clinicians and the health system?; which patients should be targeted to ensure greatest return on investment? and; what is the impact of a multi-disciplinary team in achieving the outcome/s of interest? These are all critical questions when attempting to deliver improvements, over and above usual care, in existing high-quality primary health care systems. That is, how much benefit, if any, will patients see in terms of independence, quality of life and/or hospitalisations for the resources invested, and are these outcomes considered most important to patients? The answers to these questions remain unclear for this GP-lead deprescribing intervention.

9.6 Conclusion

Consistent with the overarching study aim, a multifaceted GP-led intervention to minimise potentially inappropriate polypharmacy in community living older people, addressing key barriers to change, was shown to be feasible in the short-term and conferred a statistically significant but clinically modest deprescribing effect. Both GPs and patients reported value in the process of medication review, irrespective of the deprescribing outcome. Further research into the long-term safety and effectiveness of deprescribing interventions targeting community living older people with polypharmacy is urgently needed. Facilitating any type of practice change, however, is difficult. In optimising the adoption of a complex deprescribing intervention within larger-scale, longer-term trials, the learnings from this feasibility study must be taken into account.

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Appendix 1. Ethics approvals

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	An Exploration of GPs' and Accredited Pharmacists' Views of Deprescribing in Community Based, Older People with Polypharmacy
Chief Investigator:	Ms Kristen Anderson
Supervisor:	A/Prof Ian Scott, A/Prof Danielle Stowasser, Dr Christopher Freeman
Co-Investigator(s):	A/Prof Ian Scott, A/Prof Danielle Stowasser, Dr Christopher Freeman
School(s):	School of Medicine
Approval Number:	2014001296
Granting Agency/Degree:	NHMRC CRE Primary Quality & Safety in Integrated Primary Secondary Care
Duration:	30th September 2016

Comments/Conditions:

Expedited Review - Low Risk

Prior approval from site required to place advertising

Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Behavioural & Social Sciences Ethical Review Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Associate Professor John McLean
Chairperson
Behavioural & Social Sciences Ethical Review Committee

Signature JPM Date 24/9/2014

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Optimising Medicines Through Deprescribing in Community-Based, Older People with Polypharmacy - an Exploratory Mixed-Methods Study
Chief Investigator:	Ms Kristen Anderson
Supervisor:	A/Prof Ian Scott, A/Prof Michele Foster, Dr Danielle Stowasser, Dr Christopher Freeman
Co-Investigator(s):	A/Prof Ian Scott, A/Prof Michele Foster, Dr Danielle Stowasser, Dr Christopher Freeman
School(s):	School of Medicine; School of Pharmacy; School of Social Work & Human Services
Approval Number:	2015000044
Granting Agency/Degree:	NHMRC CRE Primary Quality & Safety in Integrated Primary Secondary Care
Duration:	30th September 2016

Comments/Conditions:

Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Signature _____ Date 4 Mar 2015

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Optimising Medicines Through Deprescribing in Community-Based, Older People with Polypharmacy - an Exploratory Mixed-Methods Study - 06/07/2015 - AMENDMENT
Chief Investigator:	Ms Kristen Anderson
Supervisor:	A/Prof Ian Scott, A/Prof Michele Foster, Dr Danielle Stowasser, Dr Christopher Freeman
Co-Investigator(s):	A/Prof Ian Scott, A/Prof Michele Foster, Dr Danielle Stowasser, Dr Christopher Freeman
School(s):	School of Medicine; School of Pharmacy; School of Social Work & Human Services
Approval Number:	2015000044
Granting Agency/Degree:	NHMRC CRE Primary Quality & Safety in Integrated Primary Secondary Care
Duration:	30th September 2016

Comments/Conditions:

Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Signature  Date 15/7/2014

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Optimising Medicines Through Deprescribing in Community-Based, Older People with Polypharmacy - an Exploratory Mixed-Methods Study - 23/11/2015 - AMENDMENT
Chief Investigator:	Ms Kristen Anderson
Supervisor:	A/Prof Ian Scott, A/Prof Michele Foster, Dr Danielle Stowasser, Dr Christopher Freeman
Co-Investigator(s):	A/Prof Ian Scott, A/Prof Michele Foster, Dr Danielle Stowasser, Dr Christopher Freeman
School(s):	School of Medicine; School of Pharmacy; School of Social Work & Human Services
Approval Number:	2015000044
Granting Agency/Degree:	NHMRC CRE Primary Quality & Safety in Integrated Primary Secondary Care
Duration:	30th September 2016

Comments/Conditions:

Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Signature _____ Date 1 Dec 2015

Appendix 2. The CEASE deprescribing framework

Current medicines – ascertain all medicines the patient is currently taking and the reasons for each one (also termed medication reconciliation).

Elevated risk – consider the potential for this patient to be harmed by the medicines being prescribed in determining required intensity of deprescribing intervention:

> Consider risk factors such as total number of drugs, age, presence of drugs associated with high risk (e.g. opiates, benzodiazepines, psychotropics, anticoagulants, hypoglycaemic drugs, cardiovascular drugs), past non-adherence, multiple prescribers, impaired cognition and poor social support, substance abuse, mental health problems.

Assess each medicine for its usefulness in relation to its risk by considering:

> Indications for the drug (is the continued prescribing of the drug justified on the basis of a verified diagnosis and robust evidence of effectiveness for this indication in this patient?);
>
> Effects of the drug to date on the underlying disease process and/or its symptoms;
>
> Future benefit–harm trade-offs in the context of life expectancy, time until benefit (for preventive medications), goals of care (symptom relief vs disease modification vs cure), and patient values and preferences.

Sort – prioritise those medicines for discontinuation with lowest utility (or highest disutility) and greatest ease of discontinuation, while taking patient preferences into account.

Eliminate – implement a discontinuation regimen, and monitor patients closely for improvement in outcomes or onset of withdrawal or rebound syndromes.

Appendix 3. Suspected adverse effect/experience from deprescribing one or more medications form

Date

Patient name & DOB

Medication/s reduced or ceased |Date reduced or ceased | Reason for deprescribing

Description of patient adverse effect/experience, including time in relation to medication changes *(please be as detailed as possible)*

Action taken to manage the adverse effect/experience

Clinical outcome *(for each subheading below please delete the response/s that do not apply)*

Current status: **(Recovered [date] | Not yet recovered | Other)**

***Seriousness of the effect/experience*: (Life threatening | Hospitalised | Required visit to doctor | Other (e.g. Phone call)**

Attribution to deprescribing

In your expert opinion, do you feel that this adverse effect/experience was in any way related to deprescribing?

Yes / No (*If yes, please provide as much detail as possible)*

Please contact Kristen Anderson – via email <provided> or via mobile <provided> upon completion. Please contact her urgently in the case of any event which was life-threatening or led to hospitalisation.

Appendix 4. Search strategy for qualitative systematic review

PubMed 22 Feb 2014 - 712 search results

((((((((((withdraw OR withdrawing OR withdrawal OR cease OR ceasing OR cessation OR stop OR stopping OR discontinue OR discontinuing OR discontinuation OR reduce OR reducing OR reduction OR deprescribe OR deprescribing OR optim*)) AND (“Prescription drug” OR medicines OR medication OR polypharmacy OR prescribing))) OR inappropriate prescribing)) AND ((Physician OR “family physician” OR “general practitioner” OR GP OR doctor OR clinician OR prescriber OR specialist OR health personnel OR "health professional" OR "health care professional" OR "health practitioner"))) AND ((((((“semi-structured”[TIAB] OR semistructured[TIAB] OR unstructured[TIAB] OR informal[TIAB] OR “in-depth”[TIAB] OR indepth[TIAB] OR “face-to-face”[TIAB] OR structured[TIAB] OR guide[TIAB] OR guides[TIAB]) AND (interview*[TIAB] OR discussion*[TIAB] OR questionnaire*[TIAB])) OR (“focus group”[TIAB] OR “focus groups”[TIAB] OR qualitative[TIAB] OR fieldwork[TIAB] OR “field work”[TIAB] OR “key informant”[TIAB])) OR “interviews as topic”[Mesh] OR “focus groups”[Mesh] OR narration[Mesh] OR qualitative research[Mesh]))))))))))

Embase 24 Feb 2014 - 1786 search results

interview:ab,ti OR discussion:ab,ti OR questionnaire:ab,ti OR survey:ab,ti OR 'focus group':ab,ti OR 'focus groups':ab,ti OR qualitative:ab,ti OR 'qualitative research'/de AND [english]/lim AND [embase]/lim
AND
['inappropriate prescribing'/de OR (inappropriate:ab,ti AND prescribing:ab,ti) AND [english]/lim AND [embase]/lim
OR
(withdraw:ab,ti OR withdrawing:ab,ti OR withdrawal:ab,ti OR cease:ab,ti OR ceasing:ab,ti OR cessation:ab,ti OR stop:ab,ti OR stopping:ab,ti OR discontinue:ab,ti OR discontinuing:ab,ti OR discontinuation:ab,ti OR reduce:ab,ti OR reducing:ab,ti OR reduction:ab,ti ORdeprescribe:ab,ti OR deprescribing:ab,ti OR optim*:ab,ti AND [english]/lim AND [embase]/lim
AND
'prescription drug'/de OR medicines:ab,ti OR medication:ab,ti OR polypharmacy:ab,ti OR prescribing:ab,ti AND [english]/lim AND [embase]/lim)]
AND
physician:ab,ti OR 'family physician':ab,ti OR 'general practitioner':ab,ti OR gp:ab,ti OR doctor:ab,ti OR clinician:ab,ti OR prescriber:ab,ti OR 'medical specialist':ab,ti OR specialist:ab,ti OR 'health care personnel':ab,ti OR 'health professional':ab,ti OR 'health care professional':ab,ti OR 'health practitioner':ab,ti AND [english]/lim AND [embase]/lim

Scopus 12 Mar 2014 - 1966 search results

(TITLE(physician OR "family physician" OR "general practitioner" OR GP OR doctor OR clinician OR prescriber OR specialist OR "health professional" OR "health care professional" OR "health personnel" OR "health practitioner" OR nurse OR pharmacist) AND SUBJAREA(MULT OR MEDI OR NURS OR VETE OR DENT OR HEAL)) AND (TITLE-ABS-KEY(interview OR discussion OR questionnaire OR survey OR "focus group" OR "focus groups" OR qualitative OR "qualitative research") AND SUBJAREA(MULT OR MEDI OR NURS OR VETE OR DENT OR HEAL)) AND (((TITLE-ABS-KEY(Withdraw OR withdrawing OR withdrawal OR cease OR ceasing OR cessation OR stop OR stopping OR discontinue OR discontinuing OR discontinuation OR reduce OR reducing OR reduction OR deprescribe OR deprescribing OR optim*) AND SUBJAREA(MULT OR MEDI OR NURS OR VETE OR DENT OR HEAL)) AND (TITLE-ABS-KEY("Prescription drug" OR

prescribing OR medicines OR medication OR polypharmacy) AND SUBJAREA(MULT OR MEDI OR NURS OR VETE OR DENT OR HEAL))) OR (TITLE-ABS-KEY(inappropriate AND prescribing) AND SUBJAREA(MULT OR MEDI OR NURS OR VETE OR DENT OR HEAL)))

CINAHL 20 Mar 2014 - 458 search results

Physician or "family physician" or "general practitioner" or GP or doctor or clinician or prescriber or specialist or "health professional" or "health care professional" OR "health personnel" or "health practitioner"
AND
("inappropriate prescribing" OR (inappropriate and prescribing)
OR
("prescription drug" OR prescribing OR medicines OR medication OR polypharmacy) AND (Withdraw or withdrawing or withdrawal or cease or ceasing or cessation or stop or stopping or discontinue or discontinuing or discontinuation or reduce or reducing or reduction or deprescribe or deprescribing or optim*))
AND
interview OR discussion OR questionnaire OR survey OR "focus group" OR "focus groups" OR qualitative

PsycINFO 20 Mar 2014 - 565 search results

(((AnyField:("prescription drug" OR prescribing OR medicines OR medication OR polypharmacy)) AND (AnyField:(Withdraw or withdrawing or withdrawal or cease or ceasing or cessation or stop or stopping or discontinue or discontinuing or discontinuation or reduce or reducing or reduction or deprescribe or deprescribing or optim*))) OR (AnyField:("inappropriate prescribing" OR (inappropriate AND prescribing)))) AND (AnyField:(Physician or "family physician" or "general practitioner" or GP or doctor or clinician or prescriber or specialist or "health professional" or "health care professional" OR "health personnel" or "health practitioner")) AND (AnyField:(interview OR discussion OR questionnaire OR survey OR "focus group" OR "focus groups" OR qualitative OR "qualitative research"))

INFORMIT 20 Mar 2014 Health collection - 516 search results

((((((Withdraw OR withdrawing OR withdrawal OR cease OR ceasing OR cessation OR stop OR stopping OR discontinue OR discontinuing OR discontinuation OR reduce OR reducing OR reduction OR deprescribe OR deprescribing or optim*) AND (“Prescription drug” OR prescribing OR medicines OR medication OR polypharmacy))) OR (inappropriate and prescribing))) AND (Physician OR “family physician” OR “general practitioner” OR GP OR doctor OR clinician OR prescriber OR specialist OR “health professional” OR “health care professional” OR "health personnel" OR “health practitioner” OR nurse or pharmacist) AND (interview OR discussion OR questionnaire OR “survey” OR “focus group” OR “focus groups” OR qualitative))

Appendix 5. Completed COREQ assessment for each study

Comprehensiveness of reporting assessment using COREQ (consolidated criteria for reporting qualitative research) checklist.
Key – Benzo = Benzodiazepines. CME = Continuing Medical Education. F = Female. FG = Focus group. Dept = Department. GP = General Practitioner. M = Male. MD = Medical doctor. NH = Nursing home. NP = Nurse Practitioner. NS = Not stated. PhD = Doctor of Philosophy. PIP = Potentially inappropriate prescribing. RCT = Randomised Control Trial. SSI = Semi-structure interview. VA = Veterans Affairs. Other abbreviations refer to study author initials.

		Lead author	Anthierens	Britten -	Cantrill	Clyne	Cook	Damesto y	Dickinson	Dybwad	Flick	Frich	Fried	Iden	Illiffe	Moen	Parr	Raghunath	Rogers	Schuling	Spinewine	Subejl	Wermeling
Domain 1: Research team and reflexivity																							
Personal Characteristics																							
1	Interviewer/facilitator	Which author/s conducted the interview or focus group?	Yes - AT collected data. T Strobbe took and processed interviews	N/A Descriptive survey	JD	FG - MB& BC, SSI - BC	JMC	NS	NS	TBD	NS	JCF & SH	TRF	KI	NS - 2 researchers	Ring	JP	ASR did 1, 'Non-clinicians' did remaining 4	NS	HJG & JS (observer)	AS	NS	GB
2	Credentials	What were the researcher's credentials? *E.g. PhD, MD*	NS	Masters, MD	Masters	NS	PhD	MD, PhD & Masters	Masters, PhD, MD, Psychiatrists	MD	NS	MD qualification as a minimum	MD	MD qualification as a minimum	NS	PhD	NS	NS	Professor of sociology, Clinical Psychologist & researcher, 3 med stude	NS - ? MD	PhD min	NS	NS

																		nts, 1 GP & Senior lecturer				
3	Occupation	What was their occupation at the time of the study?	NS	NS	Research pharmacist	NS	Research psychologist	NS	Researchers, academics, clinicians	GP – 'Important as they were peers'	NS	NS	NS	All are specialists in family medicine, experienced GPs	NS	NS	NS	NS - 1 clinician, remaining authors were not	See above	NS	Clinical pharmacist & research fellow	NS	NS
4	Gender	Was the researcher male or female?	Y - could be derived	NS	F	F	F	F	NS	F	M	F	F	F	NS	F	F	NS	Mix	M	F	NS	F
5	Experience and training	What experience or training did the researcher have?	NS	NS	NS	NS	Experienced research psychologist, specialist in geriatrics & dissemination	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	Inferred	NS	NS	NS	NS

Relationship with participants																						
6	Relationship established	Was a relationship established prior to study commencement?	NS	NS	NS	NS	NS	NS	NS	Peers - hence random selection of low-med prescribers (minimise selection bias) to match high prescriber sample	NS	NS - Run by Academic Dept GP + Norwegian Medical Association	NS	NS	Contact with practice staff when recruiting patients for SSIs	NS	NS	Mix - known and not known	NS	NS but likely - GP trainers and study conducted through Dept of General Practice at a local University	NS	Yes as this was a follow-up to a study in 2006	Follow-up to cross-sectional observation study so some familiarity
7	Participant knowledge of the interviewer	What did the participants know about the researcher? e.*g. personal goals, reasons for doing the research*	NS	NS	NS	NS	NS	NS	NS	Peers + Qualitative study accompanied survey of all prescriptions for Benzos and opiates in Oslo revealing prescribing profile	NS	NS - Some participants had prior knowledge of the project.	NS	NS	Practices had been recruited into an RCT of Benzo withdrawal in long-term users	NS	NS	NS	NS	NS	NS - Although Spinewine is well published in this space	Have insight from previous study	NS

										of every Dr in area-participants would have had an idea about researchers' interests and motivations													
8	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. *Bias, assumptions, reasons and interests in the research topic*	NS	NS	NS	NS	Specialist in geriatrics & dissemination	NS	NS	NS	NS	Interest in continuing medical education & quality care	NS	First author has long experience as NH Dr, concerned about improving health care in NHs.	NS	NS	NS	NS	All had interest in mental health.	NS	NS	NS	NS
Domain 2: Study design																							
Theoretical framework																							

9	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? *e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis*	Qual descriptive methodology, content analysis	NS	NS	Thematic analysis	Narrative analysis	Grounded theory analysis	Framework analysis	Phenomenological theory	Thematic coding – presume analysis?	Thematic content analysis	Content analysis	Systematic text condensation & analysis	NS	Conventional context analysis	Consensual Qualitative Research Approach	Grounded theory & constant comparative approach	NS (Infer grounded theory - exploratory qualitative study)	NS	Grounded theory	NS	Framework analysis
Participant selection																							
10	Sampling	How were participants selected? *e.g. purposive, convenience, consecutive, snowball*	Purposive	Convenience	Purposive sampling of practices (across 4 health authorities) & patients with	Convenience sample of GPs working in a variety of different general practices involved in a	Purposive? "deliberate efforts to diversify experience level and practice setting"	Convenience	Drs of patients purposively selected for study	Purposive (high Prescribers selected based on script volume, low-medium prescribers matched by geography etc	Convenience - physicians attached to NHs who delivered the routine data arm of	Purposive - varied sample of GPs	Purposive - sample practices from academic, community & VA settings	Purposive - 24 informants from 23 NHs	Convenience sample of practice staff involved in care of 192 patients who agreed to participate	Purposively selected existing Further education and Quality groups - already functioning forum	Convenience	Mix - Purposive & convenience	Purposive - respondents drawn from sampling frame of 70 GPs who participate/ host undergrad	Purposive - see above	Purposive - teaching & non-teaching, rural & urban hospital	Purposive - high and low Prescribers based on results of previous study	Purposive, informed by previous study

					in large practices	local CME discussion group				and then selected randomly	study				in the study	s for discussion			training				
11	Method of approach	How were participants approached? e.*g. face-to-face, telephone, mail, email*	Initial letter, follow-up telephone	NS	Letter via senior partner. Practice to ID two partners	NS	Word-of-mouth, postal mailings, phone solicitations	NS	GPs approached by letter	Letter	Via NHs with phone follow-up - necessary to discuss the project due to physician hesitancy	Approached GPs through group coordinator and contacted by phone or email.	NS	Face-to-face at professional meetings, email and nurses through calls to NHs.	NS - Recruited from PC research and teaching network of the Dept. of primary care and population studies of the Royal Free and UCL Med School	Through contacts at primary care centres in 3 large cities in Sweden	Division of General Practice newsletters, Flyers at workshops, individual faxes	NS	NS	NS	Telephone & email	Asked (?face-to-face) and then telephone follow-up required to encourage high Prescribers to participate	Letter and follow-up phone call

12	Sample size	How many participants were in the study?	65	7	22 GPs, 101 patients, 227 instances of PIP	8FG, 5 SSI	33	9	10	38	20	39 GPs (20 tutors)	36 physicians (2 NPs, 1 pharmacist, 1 physician assistant), primary care, Vet Affairs and academia	16 physicians (8 Nurses)	72 Drs/83 practice staff (from 25 practices), 192 patients	31	28 GPs	49GPs	22	29	5 Drs (4 nurses, 3 pharm, 17pts)	10 family physicians, primary care (5 high, 5 low)	10 GPs (5 high continuers, 5 low continuers)
13	Non-participation	How many people refused to participate or dropped out? Reasons?	37, Not stated	NS	NS	NS	NS	3 - None provided	5 - One retired, 2 PT, 2 no reason	High prescribers - 5 - time constraints; Med-low 10% - not stated.	NS	NS - 39/454 GPs, 20/80 Tutors	NS	NS	NS	NS	Advertised participation. Guessing must have responded and 8 declined. Reasons	18 - NS	NS	NS	NS - ?None	13 of the high Prescribers refused - 6 sick leave, 7 mainly due to time	NS

																	not stated						
Setting																							
14	Setting of data collection	Where was the data collected? e.*g. home, work*	Workplace	Workplace	Workplace	NS	NS	NS	NS	Workplace	NS	NS	NS	NS	Work place	Where groups usually met	Workplace	NS	Work place	Dept GP Uni Med Centre Groningen	NS	Workplace	Workplace
15	Presence of non-participants	Was anyone else present besides the participants and researchers?	NS	N/A Descriptive survey	NS	NS	NS	NS	NS	No	NS	NS	NS	No?	NS	NS	NS	NS	NS	NS	NS	NS	NS
16	Description of sample	What are the important characteristics of the sample? *e.g. demographic data, date*	Gender, average age, 'variety' experience and location	Role, qualification and years since qualification	NS	NS - sample of GPs working in a variety of different general practices, involved in a local CME disc	22 men, 11 women, Mean age 47, 29 Caucasian, 3 East Indian, 1 Asian, practice char	NS although gathered	GPs of patients recruited from one Primary Care Trust. Age range 34-60. 6M, 4F. No further	Info gathered 1994-1995. FT Prescribers. Higher Prescribers all male, on average older (5yrs), 5 more years in practice	NH Physicians 36-68 years, 16 NH in German city. Contracted or employed. Data collected	GPs in Norway who enrolled in CME program. 21/39 men. Med age 47.	36 physicians (2 NPs, 1 pharmacist, 1 physician assistant), primary care, Vet	Data collected 2009-2010. Diverse with respires to age, gender, profession, clinical expe	NS - Urban London Drs interested in participating in an RCT	31 GPs (4 private, 27 county-employed), aged 33-63, 15 men/ 16women, mean work experience 22	20 males, 8 females. 22 from group practices, 2 solo, 4 other settings. Ave yrs practice =	33 M, 16 F. Age range 26-62. Mix registrars, trainers-non-trainers, academic/ non-academic, inner city/ur	15 M, 7 F, mix newly registered & experienced (although biased towards younger GPs), sole and large	Dec10 - Jan11. GPs trainers, min 5 yrs experience & third year trainee in practice at the time of study. Only 2 females.	3 Drs geriatricians, 2 house officers. Summary table provided in article.	All high prescribers - male, 10yrs older than low, prescribers, 18 yrs mean employm	6 M, 4 F.2009.

						ussion group	acteristics		information provided.	(18.4 vs 13.1). Specialist education - 50% of high Prescribers, 85% med-low Prescribers. Some higher Prescribers had good reputations, some elected reps	2009.		Affairs and academia.	rience (1-40yrs) and position. FT and PT prescribers		yrs, Sweden	14. Mix rurality	ban/rural)	group GPs, mostly urban	Mean age 54 (39-65). Mix urban/rural.		ent, 50% specialists. Low prescribers - 3 males, 2 females, 12 yrs mean employment, 80% specialists). Info gathered in 2008	
Data collection																						
17	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Yes, Not tested but iterative approach subsequent to debriefing sessions	Yes, but not tested	Appropriate prescribing indicators were provided	N	Y	Y - NS	Yes & Unsure	Yes & NS. Q's served as checklist. Asked GPs to provide narratives of the last 3	Yes & No	Yes & new themes were fed back into later FGs	Yes	Yes & No but added 2 questions to the final FG as a result of FB	No - pragmatic approach (allowed participants to show understanding, raise	Yes & Yes	Yes	No - overview of how FG conducted but no content	No	Hypothetical case study, outlined position of GP and used question probes	Yes - published separately	Yes - Not pilot tested	No

										consultations (gap between ideal thinking and practice)				from FG's 1 &2	issues, min risk of them changing behaviour					where necessary. NS			
18	Repeat interviews	Were repeat interviews carried out? If yes, how many?	NS	N/A Descriptive survey	NS	No	No	No	No	No	No	NS	No	NS	No	No	No	No	NS	No	No	No	No
19	Audio/visual recording	Did the research use audio or visual recording to collect the data?	Audio taping	N/A Descriptive survey	Audio taping	Audio taping	Audio taping	Audio taping	Audio taping	Audio taping	Recorded (assume audio)	Digitally recorded	Audio taped	Audio taped	No	Audio taping	Audio taping	Audio taping	Audio taping	Audio taping	Audio taping	Audio taping	Audio taping	Video-taped
20	Field notes	Were field notes made during and/or after the interview or focus group?	Yes & debriefing	N/A Descriptive survey	NS	NS	NS	NS	Yes	NS	NS	Yes	NS	Yes	NS	Yes	Yes	NS	NS	NS	NS	NS	NS	NS
21	Duration	What was the duration	NS	N/A Descripti	NS	FG - NS, SSI -	NS	60-90min	NS	NS	45 min	NS	60 min	90 min	NS	60-90min	15-30 min	45-55 min	NS	2 hrs	60min	30-60 min	32 min (17-

		of the interviews or focus group?		ve survey		5-10 min																	54min range)
22	Data saturation	Was data saturation discussed?	NS	N/A Descriptive survey	NS	NS	Yes	Yes	NS	NS	NS	NS	NS	NS	NS	Yes	Yes	Yes	Yes	Yes	NS	NS	NS
23	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	NS	N/A Descriptive survey	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	Yes	NS	NS	NS	NS	NS
Domain 3: Analysis and findings																							
Data analysis																							
24	Number of data coders	How many data coders coded the data?	2	NS	1	NS	NS	NS	3 authors	1	NS	2	2 initially, then one after the coding structure had been established	3	2 members participated in discussions	2 with audit by a third	3 initially to develop domains and then 1 person thereafter	2	4 authors	2, 3rd adjudicated	2	2	1 author - blinded to which participants were in which category

25	Description of the coding tree	Did authors provide a description of the coding tree?	Yes	NS	NS	NS	No	No	Yes	Yes	Yes	Yes	Yes	Yes	NS	Yes	Yes	Yes	Yes	Yes	Yes - published separatel y.	Yes	Yes
26	Derivation of themes	Were themes identified in advance or derived from the data?	Derived	NS	Derived	NS	Derived	No clear themes	Derived	Both - Few preformed themes were used	Derived	Derived	Derived	Derived	Derived	Derived	Derived	Derived	Derived	Derived	Both - Inductive and defined descriptive codes.	Derived	In advance and derived (from responses to questions from extensive literature review)
27	Software	What software, if applicable, was used to manage the data?	N/A	NS	N/A	NVivo	QS N Vivo 2.0	N/A	NVivo 7	N/A	N/A	NS	NS	NS	N/A	Nvivo 1.2	NS	QSR NUD. IST 40	NS	NS	Nvivo 1.2	NS	NS
28	Participant checking	Did participants provide feedback on the findings?	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	Yes - 3 GPs did	NS	NS	NS	Yes	NS	NS

Reporting																						
29	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.*g. participant number*	Yes	No	Yes	Yes	Yes & No	No	Yes	Yes	Yes (& they were identified)	Yes	Yes & Yes	Yes - limited though and no participant number	No	Yes	Yes & No	Yes & No	Yes	Yes	Yes	Yes & Yes
30	Data and findings consistent	Was there consistency between the data presented and the findings?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Too ltd to comment	Yes - v clear	Yes - also triangulated findings with pts	Yes	Yes	Yes	Yes	Yes
31	Clarity of major themes	Were major themes clearly presented in the findings?	Yes	Yes	Yes	No - too small	Yes	No	Yes	Yes	Yes - prescriber approaches to treatment of sleep	Yes	Yes	3 clear themes although results section was limited	No	Yes - v clear	Yes	Yes	Yes	Yes	Yes	Yes

											disorders with drugs in RACF												
32	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	No	Yes but limited	No - Presented one instance of diverse views re: patient receptivity to change.	No - too small	No	No	Yes - although limited	Yes - Premise of paper to explore views of low and high Prescribers.	Yes - apparent in three subthemes of paper	No but comprehensive given diverse aims	Discussion of conflicting views and minor themes (e.g. guidelines)	Ltd information in paper	Conflicting views were presented	Yes - presented conflicting views	Yes & in methodology described these as 'typical' or variant'	Yes - captured minor themes in text but not under subheadings	Yes - presented 'outlier views'	Consistently presented counterbalancing point of view	Theory and data triangulation - stronger methodology	Captured in methodology - high and low prescribers	Captured in methodology - high and low prescribers

Appendix 6. Case study and question guides for focus group discussions

Case study and question guide - Perspectives of general practitioners and consultant pharmacists on barriers and enablers to deprescribing

We would like to use this focus group to draw on your experiences and opinions about deprescribing, or stopping or reducing medication in community living older people who are taking multiple medications but who are not terminally ill. We are not wanting to focus on those people who have already transitioned to aged care. Rather, we are looking at people who are still living in the community.

As clinicians, I don't need to tell you that there is a real tension in managing older, complex patients. Usually these individuals have a number of comorbidities and on the one hand we know medications can extend and improve quality of life. On the other hand, we know the higher the number of medications taken concurrently, the greater the risk of harms (ranging from poorer cognition and function through to hospitalisations and death).

Medications aren't started without good reason. But, as people age, and their care goals and life circumstances change, so too can the appropriateness of their therapy. So today/tonight, we are interested to hear the challenges you experience in trying to manage these complex older patients and difficulties you face when trying to rationalise therapy/make recommendations to rationalise therapy, as well as some of the things that make this process easier for you too.

To really ground our thinking in terms of the types of patients we are wanting to talk about tonight, we have a case study. We don't want to answer it. We're just using this to ground our thinking. *Introduce case study.*

Hypothetical case study - Betty, an 81-year-old lady who is a long-term patient of yours.

Adapted from: Scott IA, Gray LC, Martin JH, Mitchell CA. Minimizing inappropriate medications in older populations: a 10-step conceptual framework. American Journal of Medicine. 2012;125(6):529-37.

Past medical history

- Hypertension
- IHD with past AMI 2002 complicated by CHF
- Chronic atrial fibrillation
- Osteoporosis with past Colles' fracture
- Depression
- Osteoarthritis
- Type 2 diabetes for 15 years; past hypoglycaemia
- Renal insufficiency (CrCl 21ml/min)
- Gastro-oesophageal reflux
- Past falls (x2 last year) when walking on uneven ground
- Most recent MMSE 26/30

Functional assessment

- Lives independently in a granny flat with modifications in her daughter's house
- Able to perform basic self-cares; daughter does shopping, cooking, washing
- Limited mobility due to pain and stiffness in hips and knees; uses a wheelie-walker
- Webster pack; daughter supervises medications

Current Medications

Carvedilol 12.5mg bd
Perindopril 5mg mane
Frusemide 40mg mane
Amlodipine 5 mg mane
Spironolactone 12.5mg mane
Isosorbide mononitrate SR 60mg mane
Pravastatin 40mg mane
Digoxin 62.5microgram nocte
Warfarin 3mg nocte
Alendronate 70mg once weekly
Cholecalciferol (Ostelin®) 1000 IU day
Calcium carbonate (Caltrate®) 600mg mane
Sertraline 100mg nocte
Omeprazole 20mg bd
Gliclazide 80mg bd
Panadeine 2 tds prn
Movicol® ii bd
Oxazepam 15 mg nocte
Oxycodone 5mg tds prn

QUESTION GUIDE - GPs*. (Timing based on 60min focus group)*

OPENING (10 min)

1. Present case. What is your **initial reaction to this case**?
    a. How **typical** is this sort of patient in your practice?
    b. What are the **main challenges** you face when prescribing in a patient like Betty?

THOUGTS ABOUT BARRIERS/ENABLERS TO DEPRESCRIBING (25 minutes)

2. **How often** do you consider stopping medications in patients like Betty in your practice?
    a. *Prompt if appropriate* - So stopping medicines is something we all seem to agree with in principle, but **is it practical to be thinking about or actually be stopping medications all the time in your practice**?

3. What are the **main things that push you to consider** stopping medications in your older patients? **What things prevent you** from considering this?

4. Think of a time when you felt **really confident** stopping a medication in an older patient. What were the circumstances surrounding this?

    Now think of a time when you felt **really uncertain** about the value of stopping a medication in an older patient. What were the circumstances surrounding this?

        a. Are there particular **medications or sets of circumstances** where you find it difficult to deprescribe? Why?

5. When you stop a medication, what do you use as your guide in determining if this has been a **good thing to do**? In other words, what does success look like?

TOOLS TO DEPRESCRIBE (15 minutes)

6. What **tools or resources** do you use to assist stopping or reducing medications in your patients presently?

7. I would now like to **present to you a deprescribing framework** that could be used to assess an individual's medications to determine whether any medications are no longer necessary or are potentially harmful. This has been developed by the Australian Deprescribing Network and is currently in draft. (Give participants a few minutes to review.)

    Would you use this framework in clinical practice? Why? Why not? If not, is there anything that you could take away from this framework? What would help to facilitate the process of deprescribing?

        a. What will stop/hinder you from applying this in clinical practice?

8. What would make the process of deprescribing easier for you and your patients?

SUMMARY & CLOSE (10 minutes)

9. ***SUMMARISE.*** Of all the issues/barriers/enablers discussed, which are the most important to you? Missed anything?

QUESTION GUIDE - CPs *(Timing based on 60min focus group)*

OPENING (10 min)

1. Present case. What is your **initial reaction to this case**?
    a. How **typical** is this sort of patient when conducting home medicines reviews?
    b. What are the **main challenges** you face in undertaking a medication review in complex older, patients with excessive polypharmacy like Betty?

THOUGHTS ABOUT BARRIERS/ENABLERS TO DEPRESCRIBING (25 minutes)

2. When undertaking medication reviews, **how often** do you suggest to GPs or patients that medications be stopped or reduced?

3. What are the **main things that push you** to make a recommendation to stop or reduce medications? What **prevents you** from making a recommendation to stop or reduce medications in your patients even if you would like to?

4. **How do you feel** when making a recommendation to stop or reduce a medication which results in your -
    a. Deviating from a clinical guideline?
    b. Contradicting the advice of a specialist?
    c. What about the patients? Would you make a recommendation if the patient doesn't want to stop?

5. When you make a recommendation to stop a medication, **how would you know if this has been a good thing to do**?

TOOLS TO DEPRESCRIBE (15 minutes)

6. What **tools or resources** do you use to assist in deciding which medications should be stopped or reduced in your patients presently?

7. I would now like to **present to you a deprescribing framework** that can be used to assess an individual's medications to determine whether any medications are no longer necessary or are potentially harmful. Would you use this framework in clinical practice? Why? Why not? If not, is there anything that you could take away from this framework?
    a. What will stop/hinder you from applying this in clinical practice?

8. What would make the process of deprescribing easier for you and your patients?

SUMMARY & CLOSE (10 minutes)

9. ***SUMMARISE.*** Of all the issues/barriers/enablers discussed, which are the most important to you? Missed anything?

Appendix 7. Procedure to identify eligible exploratory study participants

1. **Run medical software or PENCAT® query for all patients**
    a. Aged 65 years or older AND prescribed 8 or more medications*

    From this full list, the aim is for each GP to identify roughly 15-20 patients for 'consent to contact' by the research team. In other words, a GP does not need to review the whole patient list if it is long – they simply need to review the list consecutively starting from the top to –

2. **Identify which patients are 'yours' or 'theirs'**
3. **Exclude patients ineligible for the study**. i.e. Those who have
    a. Conditions that would preclude consent (such as confusion, cognitive impairment, mental health disorders with psychosis and/or communication difficulties)
    b. A terminal illness
    c. Had Home Medicines Review in the past 12 months
    d. **AND** document the reason for exclusion next to their name on the list

4. **Ensure remaining shortlisted patients are**
    a. Prescribed 8 or more regular medications according to the medical record
    b. Have capacity to give consent
    c. Proficient in English and own a functioning telephone

If a GP wishes to exclude patients based on other clinical grounds (e.g. patient prone to extreme anxiety when receiving phone call from strangers) we simply ask that the GP documents the reason for exclusion.

Please do not exclude patients from the list because you think they will not want to participate.

**May also exclude antibiotics or those medications with 'prn' in the directions if your medical software can facilitate such a search. Please record the total number of patients that this report generates.*

Appendix 8. Deprescribing autofill template

Short cut for use in consult notes for UQ Deprescribing Study (short cut key 'derx').

Patient attended for appointment as part of UQ study.

Medication history taken and list reconciled? Y or N? If no, why?

Each medication reviewed for utility? Y or N? If no, why?

Medications eligible for deprescribing –

- Medication, reason, GP recommended plan, plan after discussion with patient
- Medication, reason, GP recommended plan, plan after discussion with patient
- Medication, reason, GP recommended plan, plan after discussion with patient

Next appointment to be scheduled -

Reasons when CEASING medications (free text in consult notes OR select from drop down list)-

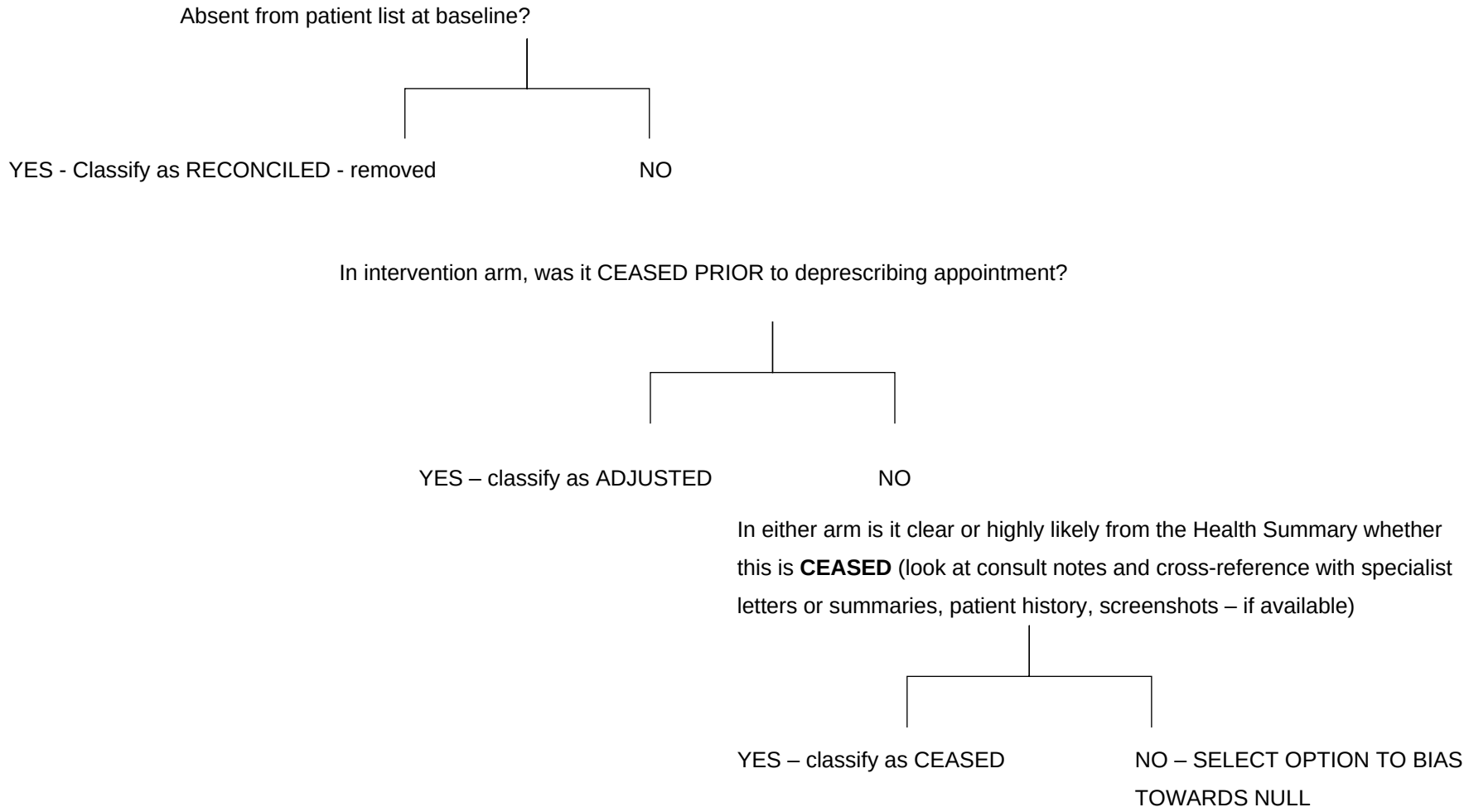
1. *No clear or valid indication (including contraindications)*
2. *Prescribing cascade*
3. *Actual or potential harms > benefits*
4. *Symptom control*
    a. *Ineffective*
    b. *Symptoms resolved*
5. *Time until benefit questionable*
6. *Unacceptable treatment burden*
7. *Patient stopped it*

Reasons when RESTARTING medications (free text in consult notes) –

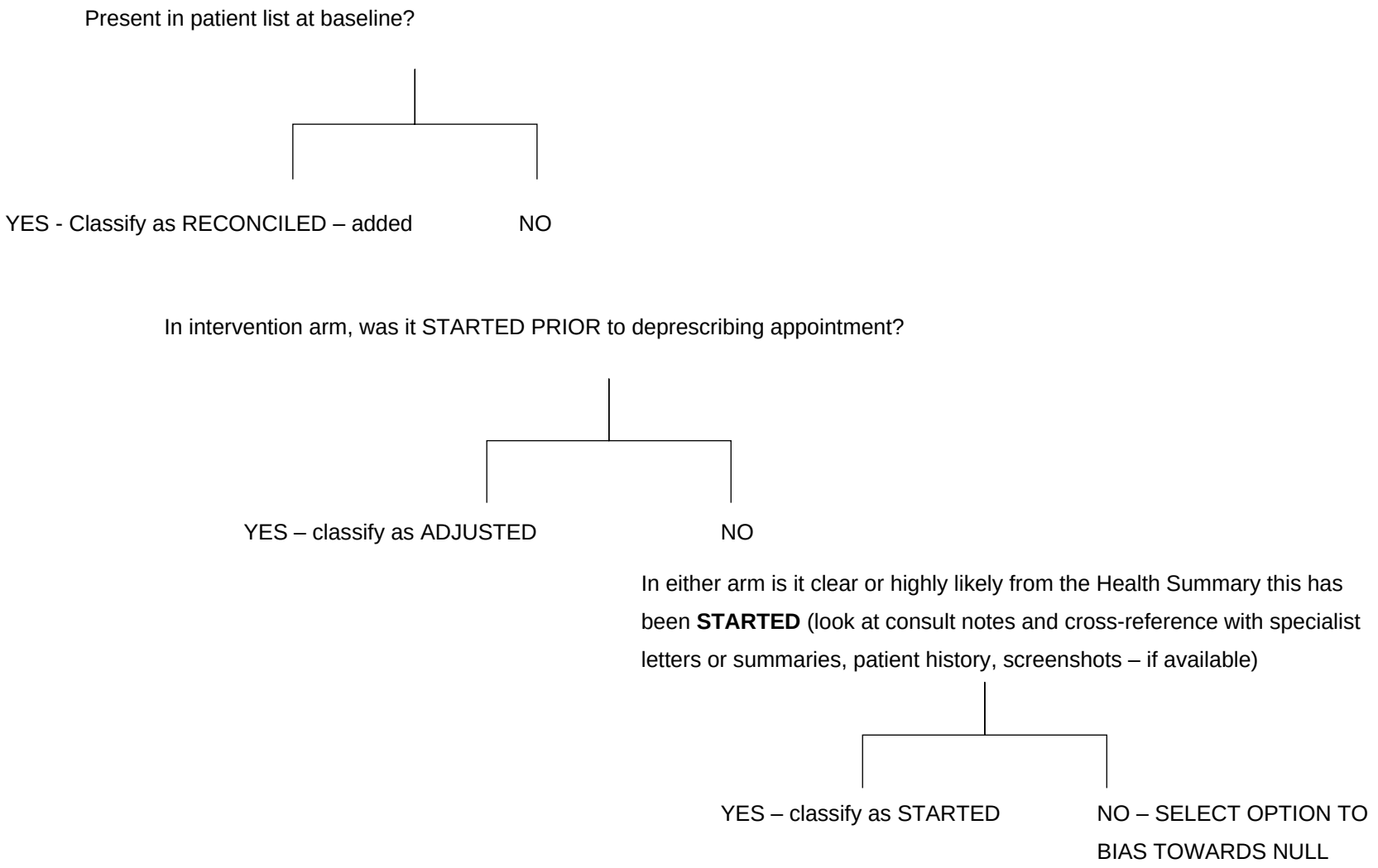
1. *Restart – Symptom relapse*
2. *Restart – Withdrawal syndrome*

Appendix 9. Process for identifying changes due to medication reconciliation

For medications **absent from** GP's medication list at follow-up (requires triangulation of GP & patient baseline & follow-up lists)



For medications **added to** GP's medication list at follow-up (requires triangulation of GP & patient baseline & follow-up lists)



Appendix 10. Patient follow-up data collection form (telephone)

NB. Usual care patients were <u>not</u> questioned about PATD or the intervention.

Hello <insert patient name>

It's <insert own name> phoning from the School of Medicine at the University of Qld. (If relevant, mention the name of the person who interviewed them last time). I'm phoning as scheduled to have our second phone interview as part of the study with Dr <insert usual GP's name> regarding your medicines. We are just wanting to go through the same questions as last time to see if anything has changed.

Is now still a convenient time to do this or shall I phone you back later? It will take approximately 25 minutes (Reschedule if unavailable).

Before we begin, would you have a list of your medications close to hand?

(If all ok, proceed with interview - please note start and finish time).

<table>
<tr><td>Participant ID</td><td colspan="3"></td></tr>
<tr><td>Date, time & duration of interview</td><td colspan="3"></td></tr>
<tr><td colspan="4">INTERVIEW QUESTIONS</td></tr>
<tr><td colspan="4">MEDICATIONS, MEDICATION MANAGEMENT & BELIEFS</td></tr>
<tr><td>(Look at the baseline data collection sheet)
Tell me, do you still <insert appropriate option - manage your own medications at home OR have someone help you with this>?

(For example, confirm that the patient hasn't started a Webster pack since we last spoke.)</td><td colspan="3"></td></tr>
<tr><td rowspan="6">I'd now like to ask you about your medications.

Which medications do you take that are prescribed by a doctor?</td><td>Medication</td><td>Dose</td><td>Frequency</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
</table>

FIRST PROMPT – Do you take any other medications on prescription such as eye drops, puffers, creams or injectable medicines? *After each additional medication, prompt once more.* *FINAL PROMPT –* And does this list include all the medications that are prescribed to you by all your doctors (for example, do you see any specialists or other GPs who also prescribe medications to you)?			
So, since we last spoke in (insert date of first interview), can you indicate, if there have been any changes to your prescription medications? *PROMPT –* For example, have any of your prescription medications been stopped (either by you or your doctor), have you had any new medications started or have there been changes to the dose of any of these medications? *If there have been changes* - Have you been able to (insert appropriate choice - e.g. stay off them, stay on the reduced dose etc?) I'm also interested to know what you *tried* to change as a result of that appointment?	Medication	Change & outcome (i.e. stopped but had to restart)	Who initiated this (e.g. GP or patient)
Do you take any non-prescription medications (such as over-the-counter medicines, herbal medications, or anything from a health food store or	Medication	Dose	Frequency

the health section of the supermarket)? *May have already provided this. Prompt as above but this may not be necessary if already provided.*			
So, since we last spoke <insert date>, can you indicate, if there have been any changes to the medications that you take over the counter? *PROMPT –* For example, have any of these medications been stopped (either by you or your doctor), have you had any new medications started or have you changed doses of any of these medications? *If there have been changes* - Have you been able to (insert appropriate choice - e.g. stay off them, stay on the reduced dose etc?) I'm also interested to know what you *tried* to change as a result of that appointment?	Medication	Change & outcome (i.e. stopped but had to restart)	Who initiated this (e.g. GP or patient)
I would now like to ask you some questions about how you feel about your medications and health. *Ask patient to locate the surveys.* **PATD** *If they have not retained this form, exclude question 13.*	15 Questions **(INTERVENTION PATIENTS ONLY)** 1=Strongly agree; 2=Agree; 3=Unsure; 4=Disagree; 5=Strongly disagree. Q1 Q2 Q3 Q4 Q5 Q6 Q7 Q8 Q9 Q10 Q11 – No or Yes (If yes, remain off, restart, different medication		

	Q12 – 5-10, 10-15, 15-20, 20-25, >25 Q13 – Q14 – Comfortable, uncomfortable, unsure Q15 – If one of your regular medications was stopped, what follow up would you like? Face to face appointment Phone call(s) Written information via post Written information via email I wouldn't need planned follow-up. I would be happy contacting a health professional if I had any problems
QUALITY OF LIFE - EQ-5D-5L *(Administer as scripted)*	See separate attachment.
MEDICAL SPECIALISTS	
Are you under the care of any medical specialists? If yes – Which specialists and how often do you see them? If no – PROMPT - so you don't see any specialists on a regular basis (e.g. heart specialist every 1-2 years)?	Name of doctor or specialty_____ Last visit _____ Frequency of review &/or next scheduled visit if known _____ Name of doctor or specialty_____ Last visit _____ Frequency of review &/or next scheduled visit if known _____ Name of doctor or specialty_____ Last visit _____ Frequency of review &/or next scheduled visit if known _____ Name of doctor or specialty_____ Last visit _____ Frequency of review &/or next scheduled visit if known _____
HOSPITAL PRESENTATIONS/ADMISSIONS	
Since we last spoke <insert date>, have you presented to a hospital emergency department for your own medical care or stayed in hospital for at least one night? How many times?	

Could you briefly describe the reason for these presentations/admissions?	
MEDICATION REVIEW	
Since we last spoke <insert date>, have you had a pharmacist come to your home to review your medicines and write a report to your GP? This is known as a Home Medicines Review. If yes – note number of times and most recent HMR date (approximations are fine).	
QUESTIONS FOR INTERVENTION PATIENTS ONLY	

Before we finish, I am interested in getting some general feedback from you regarding the appointment you had with your GP to review your medicines for appropriateness.

Just to make sure I've met the University of Queensland's requirements I will read the next bit out word for word so it might sound a bit stilted but it's the easiest way of doing it and then we know we've done it correctly.

With your permission, I would like to audio-record this part of our conversation. Each person will have their own unique experience which will provide us with valuable feedback and for this reason it is important that I record this section of the interview so I can document your personal experience accurately. Please be assured that, like all the information you have given me, you will not be identifiable from the transcript of this recording in any way. Any identifying information recorded, including your and your GP's name will be deleted from the transcript that we make from this recording. So <insert patient name>, do we have your consent to audio record your responses to the next few questions?

If yes, start recording and repeat –I've read the consent statement, do we have your consent to audio record your responses to the next few questions?

[If No to questions and recording, thank them and end call.]

Questions –

As part of your participating in this study, you had an appointment with your GP <insert date> to have a thorough review of your medicines

Can you tell me what happened in that appointment?

So how did you find that appointment (or process of the doctor going through your medicines)?

If limited response from the patient, 'Can you expand by what you mean by that'?

So it sounds like, Dr x <did/didn't> spend the time to discuss your medication. Did you feel that there was the adequate opportunity to ask questions and discuss any concerns you might have regarding your medications?

If medications were reduced or stopped or changed -

So you mentioned that as a result of the appointment, you <insert change>. When you left, did you think you would be able to manage that change?

(If positive response – challenge) ***So you didn't have any concerns about <e.g. stopping/starting/changing etc x, y or z)?***

Have those changes to your medicines had any impact on your ability to manage your medicines?

(If relevant, delve further regarding their involvement in appointment, confidence to make the changes and whether to make it easier or harder to make the changes.)

Do you have any other general feedback or comments to make before we stop recording?

Thank you very much for your time. STOP RECORDING

Appendix 11. Practice baseline data collection form

Please complete the following information as accurately as possible –

Practice Name		
Practice Principal/s		
Practice Manager		
Accreditation status (please circle)	Accredited In the process of gaining accreditation Not accredited	
Software Used (please circle)	Best Practice® or Medical Director®	
Please specify the number of individuals (i.e. headcount) and number of full time equivalents (FTE*) for each type of professional **Each FTE is defined as working 35-45 hours per week, so 2 GPs each working 20hrs/week would be recorded as 2 individual GPs and 1 FTE.*	No. of individuals	No. FTEs
GPs		
Enrolled nurses		
Registered nurses		
Nurse practitioners		
Which of the following health services, if any, are on-site at your practice? (Please tick the applicable option/s)		
Dietitian		
Imaging		
Non-dispensing pharmacist		
Pathology collection centre/lab		
Physiotherapist		
Podiatrist		
Psychologist		
Specialist(s) (specify)		
Other(s) (specify)		
NONE		

Number of active patients at the practice *(As per RACGP's definition of a patient having attended the practice three or more times in the past 2 years)*	Number_____ How did you calculate this? (Please circle) • Practice software query • PENCAT® query • Estimation • Other_____
Number of active patients who are 65 years or older	Number_____ How did you calculate this? (Please circle) • Practice software query • PENCAT® query • Estimation • Other_____
Number of active patients 65 years or older who are prescribed 8 or more regular medications	Number_____ How did you calculate this? (Please circle) • Practice software query • PENCAT® query • Estimation • Other_____

Please indicate the usual billing practices for the following patient groups in your practice -

- General _____
- Concession card holder_____
- Aged pensioner_____
- Disability pensioner_____
- Children_____
- Other (please specify)_____

Appendix 12. GP questionnaire

Minimising potentially inappropriate polypharmacy in community living, older people – an exploratory mixed-methods study

1. Name (optional)_____

2. Gender _____

3. Age _____

4. Country of graduation (primary medical degree)

   ☐ Australia ☐ Other (please specify) _____

5. How many years have you been registered as a General Practitioner? (Please specify time and if you hold a FRACGP and/or FRACRRM) _____

   OR ☐ I am a General Practice registrar (i.e. in training).

6. Please list any subspecialties

   _____

7. How many direct patient care hours do you work per week? (Include hours of direct patient care, instructions, counselling etc and other services such as referrals, prescriptions, phone calls etc). _____

Appendix 13. Post-Intervention GP interview guide

Purpose of the interviews is to explore the impact and acceptability of deprescribing intervention.

1. General opening question regarding experience participating in the study

How have you found the overall experience of participating in this study?

2. Identification of high risk patients

How did you find the process of identifying high risk patients for the deprescribing intervention?

3. Workshop on deprescribing

How adequate was the workshop in preparing you for the deprescribing intervention?

Following your experience of deprescribing, are there other issues/topics/information that should be covered in future workshops?

What are your thoughts about further follow-up/support after the workshop?

4. Deprescribing in practice

In general, what was your experience of applying the deprescribing intervention in practice?

What would you say were the consequences of the deprescribing intervention for your interactions with patients?

What sorts of changes for your patients did you see as a result of the deprescribing intervention?

- *Specifically prompt for negative and positive example – draw on patient data.*

What would you say were the consequences of the deprescribing intervention for your workload (initial and ongoing)?

5. Influence on general practice

Has this experience affected your initiation or cessation of medications in other patient groups? If so, how?

Have you shared your experience with other people in your practice?

What did you do?

6. Acceptability

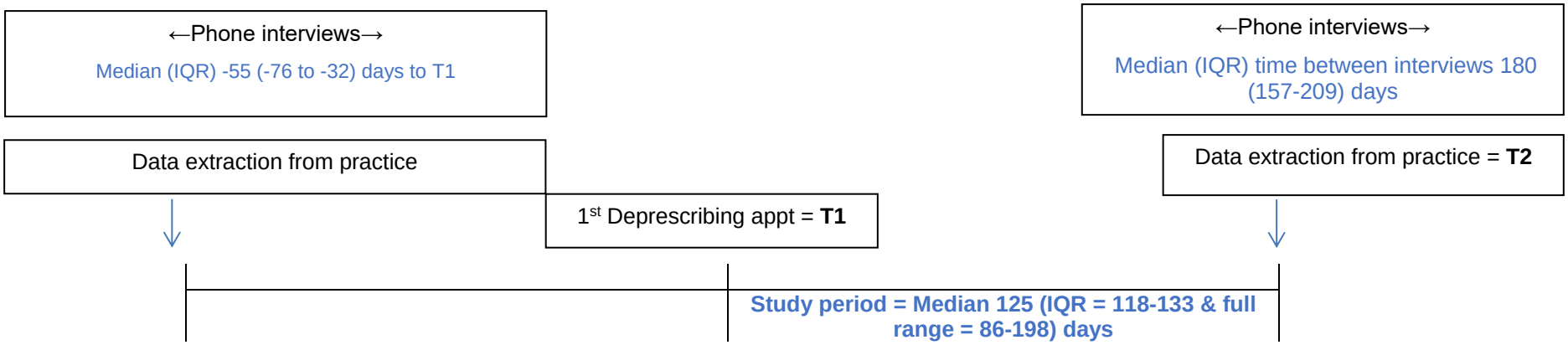
As a clinician who has been involved in the deprescribing intervention, how acceptable to you is the process of the deprescribing intervention?

Overall, how acceptable to you is the workload involved in the deprescribing intervention?

What aspects of the intervention, if any, would you change?

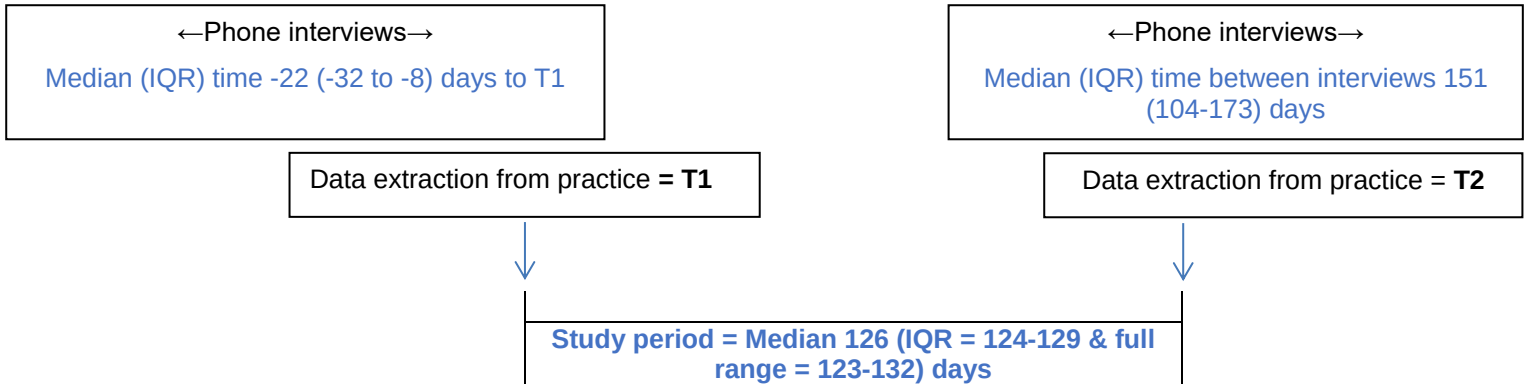
Appendix 14. Diagrammatic representation of data collection & timing

INTERVENTION GROUP



N.B. Adjusted 'Current Medication' Lists from GP consultation notes during this period, where necessary, to provide best possible baseline medication list

USUAL CARE



Appendix 15. Changes to regular medications during the study period for intervention and usual care groups

Outcome	Measure of central tendency	Intervention (SD) N=78	Usual Care (SD) N=67	IRR[a] (95%CI)	P value
Secondary Outcomes - Deprescribed[b]					
GP deprescribed	Mean	1.5 (1.697)	0.7 (1.291)	2.478 (1.518-4.047)	<0.001
	Median	1 (0-2)	0 (0-1)		
Patient-reported deprescribed	Mean	1.51 (1.475)	1 (1.393)	1.626 (1.019-2.595)	0.041
	Median	1 (0-2)	1 (0-2)		
Secondary Outcomes					
GP ceased	Mean	0.88 (1.423)	0.48 (1.223)	2.121 (1.179-3.815)	0.012
	Median	0 (0-1)	0 (0-1)		
Patient-reported ceased	Mean	0.97 (1.238)	0.63 (1.166)	1.805 (1.049-3.105)	0.033
	Median	1 (0-1.25)	0 (0-1)		
GP reduced	Mean	0.71 (0-4)	0.22 (0-2)	3.069 (1.580-5.962)	0.001e
	Median	0 (0-1)	0 (0-0)		
Patient-reported reduced	Mean	0.54 (0.848)	0.37 (0.693)	1.445 (0.877-2.381)	0.149[c,d]
	Median	0 (0-1)	0 (0-1)		
GP commenced	Mean	0.47 (0-4)	0.48 (0-4)	1.033 (0.574-1.859)	0.914
	Median	0 (0-1)	0 (0-1)		
Patient-reported commenced	Mean	0.46 (0.715)	0.81 (1.384)	0.685 (0.393-1.193)	0.181
	Median	0 (0-1)	0 (0-1)		
GP-reported unsuccessful deprescribing attempts	Mean	0.27 (0-3)	0.06 (0-2)	4.099 (1.321-12.715)	0.015[d]
	Median	0 (0-0)	0 (0-0)		
Patient-reported unsuccessful deprescribing attempts	Mean	0.32 (0.655)	0.03 (0.03)	10.236 (2.310-45.357)	0.002[d]
	Median	0 (0-0.25)	0 (0-0)		
GP increased	Mean	0.22 (0.474)	0.18 (0.424)	1.279 (0.547-2.988)	0.570
	Median	0 (0-0)	0 (0-0)		
Patient-reported increased	Mean	0.31 (0.542)	0.31 (0.583)	1.009 (0.504-2.018)	0.980
	Median	0 (0-1)	0 (0-1)		

[a] IRR - Incidence Rate Ratio (adjusted for baseline number of medications, age and gender).
[b] Includes ceased and dose-reduced medications.
[c]Possion used instead of Negative binomial regression as variance:mean <1.5.
[d]Note that the number of baseline medications did not remain a statistically significant predictor in the model.

Appendix 16. Changes to regular medications excluding supplements during the study period for intervention and usual care groups

Outcome	Measure of central tendency	Intervention (SD) N=78	Usual Care (SD) N=67	IRR[a] (95%CI)	P value
Primary Outcomes - Deprescribed [b]					
GP-reported deprescribed	Mean	1.28 (1.404)	0.66 (1.136)	2.092 (1.269-3.446)	0.004
	Median	1 (0-2)	0 (0-1)		
Patient-reported deprescribed[c]	Mean	1.14 (1.224)	0.75 (1.035)	1.596 (1.124-2.268)	0.009
	Median	1 (0-2)	0 (0-1)		
Secondary Outcomes					
GP-reported ceased	Mean	0.58 (0.961)	0.43 (1.048)	1.503 (0.815-2.772)	0.192
	Median	0 (0-1)	0 (0-1)		
Patient-reported ceased[c]	Mean	0.63 (0.913)	0.43 (0.802)	1.566 (0.980-2.503)	0.061
	Median	0 (0-1)	0 (0-1)		
GP-reported commenced	Mean	0.44 (0.749)	0.45 (0.909)	1.017 (0.555-1.861)	0.958
	Median	0 (0-1)	0 (0-1)		
Patient-reported commenced	Mean	0.32 (0.592)	0.55 (1.171)	0.713 (0.378-1.343)	0.295
	Median	0 (0-1)	0 (0-1)		

[a] IRR - Incidence Rate Ratio (adjusted for baseline number of medications, age and gender).
[b] Includes ceased and dose-reduced medications.
[c]Possion used instead of Negative binomial regression as variance:mean <1.5.

Appendix 17. Patients' Attitudes Towards Deprescribing questionnaire

Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Development and validation of the patients' attitudes towards deprescribing (PATD) questionnaire. Int J Clin Pharm. 2013;35(1):51-6.

Government of South Australia
Central Northern Adelaide Health Service

University of South Australia

Name: **Date:**

Please indicate whether or not you agree with the following statements by ticking the appropriate box.

	Strongly Agree	Agree	Unsure	Disagree	Strongly Disagree
1. I feel that I am taking a large number of medications					
2. I am comfortable with the number of medications that I am taking					
3. I believe that all my medications are necessary					
4. If my doctor said it was possible I would be willing to stop one or more of my regular medications					
5. I would like to reduce the number of medications that I am taking					
6. I feel that I may be taking one or more medications that I no longer need					
7. I would accept taking more medications for my health conditions					
8. I have a good understanding of the reasons I was prescribed each of my medications					
9. Having to pay for less medications would play a role in my willingness to stop one or more of my medications					
10. I believe one or more of my medications is giving me side effects					

11. Have you ever tried to stop a regular medication (with your doctor's knowledge)

☐ No (go to question 12) ☐ Yes - continue to next part

If Yes I was able to remain off the medication ☐

I had to restart the medication ☐

I had to be started on a different medication ☐

12. How many different tablets/capsules per day would you consider to be **a lot**? – *circle one of the below numbers*

5-10, 10-15, 15-20, 20-25, >25

1

13. What is the **MAXIMUM** number of tablets/capsules that you would be comfortable taking per day- *circle one of the below pictures*

14. How comfortable would you be if a pharmacist was involved in stopping one or more of your regular medications and provided the follow-up (informing your doctor of the progress)?

Uncomfortable ☐ Unsure ☐ Comfortable ☐

15. If one of your regular medications was stopped, what follow-up would you like?

- ☐ Face to face appointment
- ☐ Phone call(s)
- ☐ Written information via post
- ☐ Written information via email
- ☐ I wouldn't need planned follow-up. I would be happy contacting a health professional if I had any problems

Thank you for completing the questionnaire

Appendix 18. EQ-5D-5L – Telephone questionnaire

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

Health Questionnaire

English version for the UK

SCRIPT FOR TELEPHONE INTERVIEW

GENERAL INTRODUCTION

It is suggested that the telephone interviewer follows the script of the EQ-5D. Although allowance should be made for the interviewer's particular style of speaking, the wording of the questionnaire instructions should be followed as closely as possible. In the case of the EQ-5D descriptive system on pages 2 and 3, the precise wording must be followed.

It is recommended that the interviewer has a copy of the EQ-5D in front of him or her as it is administered over the telephone. This enables the respondent's answers to be entered directly on the EQ-5D by the interviewer on behalf of the respondent (i.e. the appropriate boxes on pages 2 and 3 are marked and the scale on page 4 is marked at the point indicating the respondent's 'health today'). The respondent should also have a copy of the EQ-5D in front of him or her for reference. If the respondent asks for clarification, the interviewer can help by re-reading the question verbatim. The interviewer should not try to offer his or her own explanation but suggest that the respondent uses his or her own interpretation.

If the respondent has difficulty regarding which box to mark, the interviewer should repeat the question verbatim and ask the respondent to answer in a way that most closely resembles his or her thoughts about his or her health today.

INTRODUCTION TO EQ-5D

(Note to interviewer: please read the following to the respondent)

We are trying to find out what you think about your health. I will first ask you some simple questions about your health TODAY. I will then ask you to rate your health on a measuring scale. I will explain what to do as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

EQ-5D DESCRIPTIVE SYSTEM: INTRODUCTION

First I am going to read out some questions. Each question has a choice of five answers. Please tell me which answer best describes your health TODAY. Do not choose more than one answer in each group of questions.

(Note to interviewer: it may be necessary to remind the respondent regularly that the timeframe is TODAY. It may also be necessary to repeat the questions verbatim)

EQ-5D DESCRIPTIVE SYSTEM

MOBILITY

First I'd like to ask you about mobility. Would you say that:

1. **You have no problems in walking about?**
2. **You have slight problems in walking about?**
3. **You have moderate problems in walking about?**
4. **You have severe problems in walking about?**
5. **You are unable to walk about?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

SELF-CARE

Next I'd like to ask you about self-care. Would you say that:

1. **You have no problems washing or dressing yourself?**
2. **You have slight problems washing or dressing yourself?**
3. **You have moderate problems washing or dressing yourself?**
4. **You have severe problems washing or dressing yourself?**
5. **You are unable to wash or dress yourself?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

USUAL ACTIVITIES

Next I'd like to ask you about usual activities, for example work, study, housework, family or leisure activities. Would you say that:

1. **You have no problems doing your usual activities?**
2. **You have slight problems doing your usual activities?**
3. **You have moderate problems doing your usual activities?**
4. **You have severe problems doing your usual activities?**
5. **You are unable to do your usual activities?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

PAIN / DISCOMFORT

Next I'd like to ask you about pain or discomfort. Would you say that:

1. **You have no pain or discomfort?**
2. **You have slight pain or discomfort?**
3. **You have moderate pain or discomfort?**
4. **You have severe pain or discomfort?**
5. **You have extreme pain or discomfort?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

ANXIETY / DEPRESSION

Finally I'd like to ask you about anxiety or depression. Would you say that:

1. **You are not anxious or depressed?**
2. **You are slightly anxious or depressed?**
3. **You are moderately anxious or depressed?**
4. **You are severely anxious or depressed?**
5. **You are extremely anxious or depressed?**

(Note to interviewer: mark the appropriate box on the EQ-5D questionnaire)

EQ VAS: INTRODUCTION

(Note to interviewer: if possible, it might be useful to send a visual aid (i.e. the EQ VAS) before the telephone call so that the respondent can have this in front of him or her when completing the task)

Now, I would like to ask you to say how good or bad your health is TODAY.

I'd like you to try to picture in your mind a scale that looks a bit like a thermometer. Can you do that? The best health you can imagine is marked 100 (one hundred) at the top of the scale and the worst health you can imagine is marked 0 (zero) at the bottom.

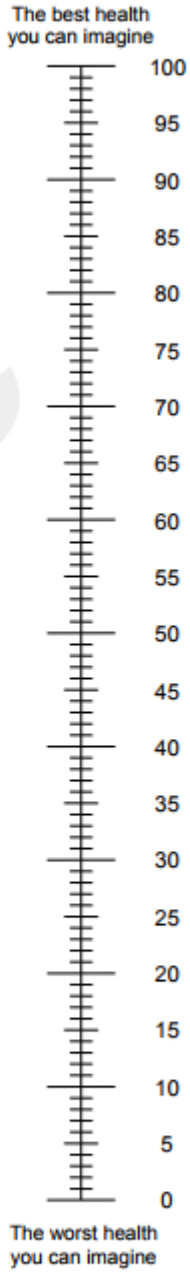
EQ VAS: TASK

I would now like you to tell me the point on this scale where you would put your health today.

(Note to interviewer: mark the scale at the point indicating the respondent's 'health today'. Now, please write the number you marked on the scale in the box below)

THE RESPONDENT'S HEALTH TODAY ☐

Thank you for taking the time to answer these questions.



Appendix 19. SPSS Output - Rotated Component Matrix and Total Variance explained from Factor Analysis of 10 PATD survey items

Rotated Component Matrix[a]

		Component			
		1	2	3	4
1.	Baseline – I feel that I am taking a large number of medications	.806			
2.	Baseline – I am comfortable with the number of medications that I am taking		.586		
3.	Baseline – I believe all my medications are necessary		.889		
4.	Baseline – If my doctor said it was possible I would be willing to stop one or more of my regular medications	.665			
5.	Baseline – I would like to reduce the number of medications that I am taking	.821			
6.	Recoded - Baseline - I feel that I may be taking one or more medicines that I no longer need		.765		
7.	Baseline – I would accept taking more medications for my health conditions			.911	
8.	Baseline - I have a good understanding if the reasons I was prescribed each of my medications			.543	
9.	Baseline – Having to pay for less medications would play a role in my willingness to stop one or more of my medications				.872
10.	Baseline – I believe one or more of my medications is giving me side effects	.584			

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization.[a]

a. Rotation converged in 6 iterations.

Total Variance Explained

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	2.651	26.513	26.513	2.651	26.513	26.513	2.476	24.757	24.757
2	1.894	18.942	45.455	1.894	18.942	45.455	1.938	19.383	44.140
3	1.294	12.945	58.400	1.294	12.945	58.400	1.285	12.854	56.994
4	1.093	10.929	69.329	1.093	10.929	69.329	1.234	12.335	69.329
5	.805	8.051	77.380						
6	.656	6.563	83.943						
7	.517	5.167	89.110						
8	.483	4.827	93.937						
9	.346	3.456	97.393						
10	.261	2.607	100.000						

Extraction Method: Principal Component Analysis.